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(71) Applicant: UNIVERSITY OF PITTSBURGH [US/US]; Office of Technology Transfer, 911 Williams Pitt Union, Pittsburgh, PA 15260 (US).

(72) Inventors: SEBTI, Said, M.; 8957 Magnolia Chase Circle, Tampa, FL 33647 (US). HAMILTON, Andrew, D.; 1 White Pine Lane, Guilford, CT 06437 (US). AUGERI, David, J.; 6846 3rd Avenue, Kenosha, WI 53143 (US). BARR, Kenneth, J.; 4828 N. Hermitage #3A, Chicago, IL 60640-4143 (US). DONNER, Bernard, G.; 1901 McRae Lane, Mundelein, IL 60060 (US). FAKHOURY, Stephen, A.; 517 Buckingham, Mundelein, IL 60060 (US). JANOWICK, David, A.; 37070 Ganster Road, Beach Park, IL 60087 (US). KALVIN, Douglas, M.; 1201 Lockwood Drive, Buffalo Grove, IL 60689 (US). LARSEN, John, J.; 10542 Altegld Street, Melrose Park, IL 60164 (US). LIU, Gang; 838 Alderly Lane, Gurnee, IL 60031 (US). O'CONNOR, Stephen, J.; 2103 Washington Avenue, Wilmette, IL 60091 (US). ROSENBERG, Saul, H.; 15 Lighthouse Lane, Grayslake, IL 60030 (US). SHEN, Wang; 6215 Formoor Lane, Gurnee, IL 60031 (US). SWENSON, Rolf, E.; 285 Penny Lane, Grayslake, IL 60030 (US). SORENSEN, Bryan, K.; 2620 North Lewis Avenue, Waukegan, IL 60087 (US). SULLIVAN, Gerard M.; 2214 North Sunrise Drive, Round lake Beach, Illinois 60073 (US). SZCZEPANKIEWICZ, Bruce G.; 33720 Royal Oake Lane, Apt. 209, Gages Lake, Illinois 60030 (US). TASKER, Andrew S.; 6251 Eagle Ridge Drive, Gurnee, Illinois 60031 (US). WASICK, James I.; 28440 Dorie Lane, Waterford, Wisconsin 53185 (US). WINN, Martin; 1263 Carlisle Place, Deerfield, Illinois 60015 (US).

(74) Agents: KOKULIS, Paul, N. et al.; Cushman Darby & Cushman, Intellectual Property Group of Pillsbury Madison & Sutro, 1100 New York Avenue, N.W., Washington, DC 20005 (US).

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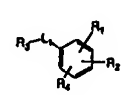
(54) Title: INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

(57) Abstract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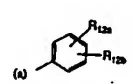
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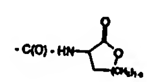
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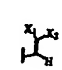
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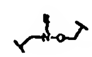
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Compounds having formula (I) or a pharmaceutically acceptable salt thereof wherein R_1 is (a) hydrogen, (b) lower alkyl, (c) alkenyl, (d) alkoxy, (e) thioalkoxy, (f) halo, (g) haloalkyl, (h) aryl $-L_2-$, and (i) heterocyclic $-L_2-$; R_2 is selected from (a) formula (1), (b) $-C(O)NH-CH(R_{14})-C(O)OR_{15}$, (c) formula (2), (d) $-C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16}$, (e) $-C(O)NH-CH(R_{14})$–tetrazolyl, (f) $-C(O)NH$–heterocyclic, and (g) $-C(O)NH-CH(R_{14})-C(O)NR_{17}R_{18}$; R_3 is substituted or unsubstituted heterocyclic or aryl, substituted or unsubstituted cycloalkyl or cycloalkenyl, formula (3), and $-P(W)R^{R3}R^{R3'}$; R_4 is hydrogen, lower alkyl, haloalkyl, halogen, aryl, arylalkyl, heterocyclic, or (heterocyclic)alkyl; L_1 is absent or is selected from (a) $-L_4-N(R_5)-L_5-$, (b) $-L_4-O-L_5-$, (c) $-L_4-S(O)_n-L_5-$, (d) $-L_4-L_6-C(W)-N(R_5)-L_5-$, (e) $-L_4-L_6-S(O)_m-N(R_5)-L_5-$, (f) $-L_4-N(R_5)-C(W)-L_7-L_5-$, (g) $-L_4-N(R_5)-S(O)_p-L_7-L_5-$, (h) optionally substituted alkylene, (i) optionally substituted alkenylene, (j) optionally substituted alkynylene, (k) a covalent bond, (l) formula (4), and (m) formula (5) are inhibitors of protein isoprenyl transferases. Also disclosed are protein isoprenyl transferase inhibiting compositions and a method of inhibiting protein isoprenyl transferases.

INHIBITORS OF PROTEIN ISOPRENYL TRANSFERASES

Technical Field

The present invention relates to novel compounds which are useful in inhibiting protein isoprenyl transferases (for example, protein farnesyltransferase and protein geranylgeranyltransferase) and the farnesylation or geranylgeranylation of the oncogene protein Ras and other related small g-proteins, compositions containing such compounds and methods of using such compounds.

Background of the Invention

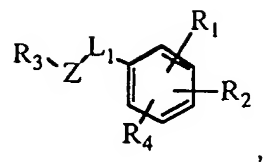
Ras oncogenes are the most frequently identified activated oncogenes in human tumors. Transformed protein Ras is involved in the proliferation of cancer cells. The Ras must be farnesylated before this proliferation can occur. Farnesylation of Ras by farnesyl pyrophosphate (FPP) is effected by protein farnesyltransferase. Inhibition of protein farnesyltransferase, and thereby farnesylation of the Ras protein, blocks the ability of transformed cells to proliferate. Inhibition of protein geranylgeranyltransferase and, thereby, of geranylgeranylation of Ras proteins, also results in down regulation of Ras protein function.

Activation of Ras and other related small g-proteins that are farnesylated and/or geranylated also partially mediates smooth muscle cell proliferation (Circulation, I-3: 88 (1993), which is hereby incorporated herein by reference). Inhibition of protein isoprenyl transferases, and thereby farnesylation or geranylgeranylation of the Ras protein, also aids in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis, a condition which compromises the success of angioplasty and surgical bypass for obstructive vascular lesions.

There is therefore a need for compounds which are inhibitors of protein farnesyltransferase and protein geranylgeranyltransferase.

Summary of the Invention

In its principle embodiment, the invention provides a compound having the formula:



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or a pharmaceutically acceptable salt thereof, wherein

R_1 is selected from the group consisting of

(1) hydrogen,
(2) alkenyl,
(3) alkynyl,
(4) alkoxy,
(5) haloalkyl,
(6) halogen,
(7) loweralkyl,
(8) thioalkoxy,
(9) aryl-L_2- wherein aryl is selected from the group consisting of
    (a) phenyl,
    (b) naphthyl,
    (c) dihydronaphthyl,
    (d) tetrahydronaphthyl,
    (e) indanyl, and
    (f) indenyl

wherein (a)-(f) are unsubstituted or substituted with at least one of X, Y, or Z wherein X, Y, and Z are independently selected from the group consisting of

alkenyl,
alkynyl,
alkoxy,
aryl,
carboxy,
cyano,
halogen,
haloalkyl,
hydroxy,
hydroxyalkyl,
loweralkyl,
nitro,

N-protected amino, and

-NRR' wherein R and and R' are independently selected from the group consisting of

hydrogen and

loweralkyl,

oxo (=O), and

thioalkoxy and

L_2 is absent or is selected from the group consisting of

$-CH_2-$,

$-CH_2CH_2-$,

$-CH(CH_3)-$,

-O-,

-C(O)-,

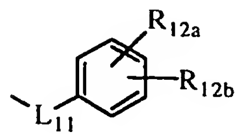
$-S(O)_q$ wherein q is 0, 1 or 2, and

-N(R)-, and

(10) heterocycle-L_2- wherein L_2 is as defined above and the heterocycle is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

(a) loweralkyl,
(b) hydroxy,
(c) hydroxyalkyl,
(d) halogen
(e) cyano,
(f) nitro,
(g) oxo (=O),
(h) -NRR',
(i) N-protected amino,
(j) alkoxy,
(k) thioalkoxy,
(l) haloalkyl,
(m) carboxy, and
(n) aryl;

R_2 is selected from the group consisting of

(1)  wherein L_{11} is selected from the group consisting of

(a) a covalent bond,

(b) -C(W)N(R)- wherein R is defined previously and W is selected from the group consisting of O and S,

(c) -C(O)-,

(d) -N(R)C(W)-,

(e) $-CH_2O-$,

(f) -C(O)O-, and

(g) $-CH_2N(R)-$,

R_{12a} is selected from the group consisting of

(a) hydrogen,

(b) loweralkyl, and

(c) $-C(O)OR_{13}$ wherein R_{13} is selected from the group consisting of

hydrogen and

a carboxy-protecting group, and

R_{12b} is selected from the group consisting of

(a) hydrogen and

(b) loweralkyl,

with the proviso that R_{12a} and R_{12b} are not both hydrogen,

(2) $-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$ wherein L_{11} is defined previously,

R_v is selected from the group consisting of

(a) hydrogen and

(b) loweralkyl,

R_{15} is selected from the group consisting of

(a) hydrogen,

(b) alkanoyloxyalkyl,

(c) loweralkyl, and

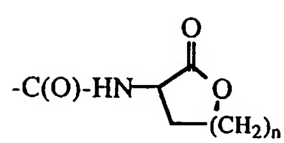
(b) a carboxy-protecting group, and

R_{14} is selected from the group consisting of

(a) alkoxyalkyl,

(b) alkoxyarylalkyl,

(c) alkoxycarbonylalkyl,
(d) alkylsulfinyalkyl,
(e) alkylsulfonylalkyl,
(f) alkynyl,
(g) aminoalkyl,
(h) aminocarbonylalkyl,
(i) aminothiocarbonylalkyl,
(j) aryl,
(k) arylalkyl,
(l) carboxyalkyl,
(m) cyanoalkyl,
(n) cycloalkyl,
(o) cycloalkylalkoxyalkyl,
(p) cycloalkylalkyl,
(q) (heterocyclic)alkyl,
(r) hydroxyalkyl,
(s) hydroxyarylalkyl,
(t) loweralkyl,
(u) sulfhydrylalkyl,
(v) thioalkoxyalkyl wherein the thioalkoxyalkyl is unsubstituted or substituted with 1, 2, 3, or 4 substituents selected from the group consisting of halogen,
(w) thioalkoxyalkylamino, and
(x) thiocycloalkyloxyalkyl,

(3)  wherein n is 1-3,

(4) -C(O)NH-CH(R_{14})-C(O)NHSO$_2$R$_{16}$ wherein R_{14} is defined previously and R_{16} is selected from the group consisting of
(a) loweralkyl,
(b) haloalkyl,
(c) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently

selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl, and

(d) heterocycle wherein the heterocycle is unsubstituted or substituted with substituents independently selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR',
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl;

(5) -C(O)NH-CH(R_{14})-tetrazolyl wherein the tetrazole ring is unsubstituted or substituted with loweralkyl or haloalkyl,

(6) -L_{11}-heterocycle,

(7) -C(O)NH-CH(R_{14})-C(O)N$R_{17}R_{18}$ wherein R_{14} is defined previously and R_{17} and R_{18} are independently selected from the group consisting of

(a) hydrogen,
(b) loweralkyl,
(c) arylalkyl,
(d) hydroxy, and
(e) dialkylaminoalkyl,

(8) -C(O)OR_{15}, and

(9) -C(O)NH-CH(R_{14})-heterocycle wherein R_{14} is as previously defined and the heterocycle is unsubstituted or substituted with loweralkyl or haloalkyl;

L_1 is absent or is selected from the group consisting of

(1) -L_4-N(R_5)-L_5- wherein L_4 is absent or selected from the group consisting of

(a) C_1-to-C_{10}-alkylene and
(b) C_2-to-C_{16}-alkenylene,

wherein the alkylene and alkenylene groups are unsubstituted or substituted with 1, 2, 3 or 4 substitutents independently selected from the group consisting of

alkenyl,
alkenyloxy,
alkenyloxyalkyl,
alkenyl[S(O)$_q$]alkyl,
alkoxy,
alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same carbon,
alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of

halogen and
cycloalkyl,
alkylsilyloxy,
alkyl[S(O)$_q$],
alkyl[S(O)$_q$]alkyl,
aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
alkoxy wherein the alkoxy is unsubstituted or substituted with substituents selected from the group consisting of cycloalkyl,
aryl,
arylalkyl,
aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of,
halogen,
nitro, and
-NRR',
cycloalkyl,
halogen,
loweralkyl,
hydroxyl,
nitro,
-NRR', and
-SO_2NRR',
arylalkoxy wherein the arylalkoxy is unsubstituted or substituted with substituents selected from the group consisting of alkoxy,
arylalkyl,
arylalkyl[S(O)$_q$]alkyl,
aryl[S(O)$_q$],
aryl[S(O)$_q$]alkyl wherein the aryl[S(O)$_q$]alkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from
alkoxy and

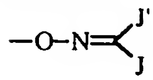
loweralkyl,
arylalkoxyalkyl wherein the arylalkoxyalkyl is unsubstituted or substituted with substituents selected from the group consisting of
alkoxy, and
halogen,
aryloxy,
aryloxyalkyl wherein the aryloxyalkyl is unsubstituted or substituted with substituents selected from the group consisting of halogen,
carboxyl,
-C(O)NR$_C$R$_D$ wherein R$_C$ and R$_D$ are independently selected from the group consisting of
hydrogen,
loweralkyl, and
alkoxycarbonyl or
R$_C$ and R$_D$ together with the nitrogen to which they are attached form a ring selected from the group consisting of
morpholine,
piperidine,
pyrrolidine
thiomorpholine,
thiomorpholine sulfone, and
thiomorpholine sulfoxide,
wherein the ring formed by R$_C$ and R$_D$ together is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of alkoxy and alkoxyalkyl,
cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of alkenyl,
cyclolalkoxy,
cycloalkoxycarbonyl,
cyclolalkoxyalkyl,

cyclolalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of aryl,
loweralkyl, and
alkanoyl,
cycloalkylalkoxy,
cycloalkylalkoxycarbonyl,
cycloalkylalkoxyalkyl,
cycloalkylalkyl,
cyclolalkyl[$S(O)_q$]alkyl,
cycloalkylalkyl[$S(O)_q$]alkyl,
fluorenyl,
heterocycle wherein the heterocycle is unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of
alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of aryl and cycloalkyl,
alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
aryl and
cycloalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of
aryl and
cycloalkyl,
aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkanoyl,
alkoxy,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
-NRR', and
thioalkoxy,
arylalkyl,
aryloxy,
cycloalkoxyalkyl,
cycloalkyl,
cycloalkylalkyl,
halogen,
heterocycle,
hydroxyl,
loweralkyl wherein the loweralkyl is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the same carbon, and
$-NR^{R3R3'}$ wherein R^{R3} and $R^{R3'}$ are independently selected from the group consisting of
hydrogen
aryl,
loweralkyl,
aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cycloalkyl, and

cycloalkylalkyl, and
sulfhydryl,
(heterocyclic)alkoxy,
(heterocyclic)alkyl,
(heterocyclic)alkyl[$S(O)_q$]alkyl,
(heterocyclic)oxy,
(heterocyclic)alkoxyalkyl,
(heterocyclic)oxyalkyl,
heterocycle[$S(O)_q$]alkyl,
hydroxyl,
hydroxyalkyl,
imino,
N-protected amino,
=N-O-aryl, and
=N-OH,
=N-O-heterocycle wherein the heterocycle is unsubstituted or substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of
loweralkyl,
hydroxy,
hydroxyalkyl,
halogen,
cyano,
nitro,
oxo (=O),
-NRR'
N-protected amino,
alkoxy,
thioalkoxy,
haloalkyl,
carboxy, and
aryl,
=N-O-loweralkyl,
$-NR^{R3}R^{R3'}$,
$-NHNR_CR_D$,
-OG wherein G is a hydroxyl protecting group,

-O-NH-R,

 wherein J and J' are independently selected from the group consisting of

loweralkyl and

arylalkyl,

oxo,

oxyamino(alkyl)carbonylalkyl,

oxyamino(arylalkyl)carbonylalkyl,

oxyaminocarbonylalkyl,

$-SO_2$-A wherein A is selected from the group consisting of

loweralkyl,

aryl, and

heterocycle

wherein the loweralkyl, aryl, and heterocycle are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

alkoxy,

halogen,

haloalkyl,

loweralkyl, and

nitro,

sulfhydryl,

thioxo, and

thioalkoxy,

L_5 is absent or selected from the group consisting of

(a) C_1-to-C_{10}-alkylene and

(b) C_2-to-C_{16}-alkenylene

wherein (a) and (b) are unsubstituted or substituted as defined previously, and

R_5 is selected from the group consisting of

hydrogen,

alkanoyl wherein the alkanoyl is unsubstituted or substituted with substituents selected from the group consisting of aryl,

alkoxy,
alkoxyalkyl,
alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2 or 3 substituents independently selected from the group consisting of
aryl and
halogen,
alkylaminocarbonylalkyl wherein the alkylaminocarbonylalkyl is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of aryl,
(anthracenyl)alkyl,
aryl,
arylalkoxy,
arylalkyl wherein the arylalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
alkoxy,
aryl,
carboxyl,
cyano,
halogen,
haloalkoxy,
haloalkyl,
nitro,
oxo, and
$-L_{11}-C(R_{14})(R_v)-C(O)OR_{15}$,
(aryl)oyl wherein the (aryl)oyl is unsubstituted or substituted with substituents selected from the group consisting of halogen,
aryloxycarbonyl,
carboxaldehyde,
-C(O)NRR',
cycloalkoxycarbonyl,

cycloalkylaminocarbonyl,

cycloalkylaminothiocarbonyl,

cyanoalkyl,

cyclolalkyl,

cycloalkylalkyl wherein the cycloalkylalkyl is unsubstituted or substituted with 1 or 2 hydroxyl substituents,

with the proviso that no two hydroxyls are attached to the same carbon,

(cyclolalkyl)oyl,

(9,10-dihydroanthracenyl)alkyl wherein the (9,10-dihydroanthracenyl)alkyl is unsubstituted or substituted with 1 or 2 oxo substituents,

haloalkyl,

heterocycle,

(heterocyclic)alkyl wherein the (heterocyclic)alkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of loweralkyl,

(heterocyclic)oyl,

loweralkyl, wherein the loweralkyl is unsubstituted or substituted with substituents selected from the group consisting of -NRR',

$-SO_2$-A, and

thioalkoxyalkyl;

(2) $-L_4$-O-L_5-,

(3) $-L_4$-S(O)$_m$-L_5- wherein L_4 and L_5 are defined previously and m is 0, 1, or 2,

(4) $-L_4$-L_6-C(W)-N(R_6)-L_5- wherein L_4, W, and L_5 are defined previously, R_6 is selected from the group consisting of

(a) hydrogen,

(b) loweralkyl,

(c) aryl,

(d) arylalkyl,

(e) heterocycle,

(f) (heterocyclic)alkyl,

(g) cyclolakyl, and

(h) cycloalkylalkyl, and

L_6 is absent or is selected from the group consisting of

(a) -O-,

(b) -S-, and

(c) -N($R_{6'}$)- wherein $R_{6'}$ is selected from the group consisting of
hydrogen,
loweralkyl,
aryl,
arylalkyl,
heterocycle,
(heterocyclic)alkyl,
cyclolakyl, and
cycloalkylalkyl,

(5) -L_4-L_6-S(O)$_m$-N(R_5)-L_5-,

(6) -L_4-L_6-N(R_5)-S(O)$_m$-L_5-,

(7) -L_4-N(R_5)-C(W)-L_7-L_5- wherein L_4, R_5, W, and and L_5 are defined previously and L_7 is absent or is selected from the group consisting of -O- and -S-,

(8) C_1-C_{10}-alkylene wherein the alkylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

(a) aryl,

(b) arylalkyl,

(c) heterocycle,

(d) (heterocyclic)alkyl,

(e) cyclolakyl,

(f) cycloalkylalkyl,

(g) alkylthioalkyl, and

(h) hydroxy,

(9) C_2-to-C_{10}-alkenylene wherein the alkenylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

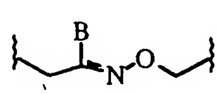
(a) aryl,
(b) arylalkyl,
(c) (aryl)oxyalkyl wherein the (aryl)oxyalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,
(d) heterocycle,
(e) (hererocycle)alkyl,
(f) hydroxyalkyl,
(g) cyclolakyl,
(h) cycloalkylalkyl,
(i) alkylthioalkyl, and
(j) hydroxy,

(10) C_2-to-C_{10}-alkynylene wherein the alkynylene group is unsubstituted or substituted with 1 or 2 substituents independently selected from the group consisting of

(a) aryl,
(b) arylalkyl,
(c) heterocycle,
(d) (heterocyclic)alkyl,
(e) cyclolakyl,
(f) cycloalkylalkyl,
(g) alkylthioalkyl, and
(h) hydroxy,

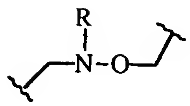
(11) -L_4-heterocycle-L_5-,

(12) a covalent bond,

(13) 

wherein B is selected from the group consisting of loweralkyl and

arylalkyl, and

(14)  ;

Z is selected from the group consisting of

(1) a covalent bond,
(2) -O-,
(3) -$S(O)_q$-, and
(4) -NR_Z- wherein R_Z is selected from the group consisting of
    (a) hydrogen
    (b) loweralkyl,
    (c) aryl,
    (d) arylalkyl,
    (e) heterocycle,
    (f) (heterocyclic)alkyl,
    (g) cyclolakyl, and
    (h) cycloalkylalkyl;

R_3 is selected from the group consisting of

(1) hydrogen,
(2) aryl,
(3) fluorenyl,
(4) heterocycle,

wherein (2)-(4) are unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of

(a) alkanoyl,
(b) alkoxy wherein the alkoxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
    halogen,
    aryl, and
    cycloalkyl,
(c) alkoxyalkyl wherein the alkoxyalkyl is unsubstituted or substituted with 1 or 2, 3, 4 or 5 substituents independently selected from the group consisting of

aryl and
cycloalkyl,

(d) alkoxycarbonyl wherein the alkoxycarbonyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
aryl, and
cycloalkyl,

(e) alkylsilyloxyalkyl,

(f) arylalkyl,

(g) aryl wherein the aryl is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of
alkanoyl,
alkoxy wherein the alkoxy is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of cycloalkyl,
carboxaldehyde,
haloalkyl,
halogen,
loweralkyl,
nitro,
-NRR', and
thioalkoxy,

(h) arylalkyl,

(i) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of,
halogen,
nitro, and
-NRR',

(j) (aryl)oyl,

(k) carboxaldehyde,

(l) carboxy,

(m) carboxyalkyl,

(n) -C(O)NRR" wherein R is defined previously.and R" is selected from the group consisting of
hydrogen,

loweralkyl, and
carboxyalkyl,

(o) cyano,
(p) cyanoalkyl,
(q) cycloalkyl,
(r) cycloalkylalkyl,
(s) cycloalkoxyalkyl,
(t) halogen,
(u) haloalkyl wherein the haloalkyl is unsubstituted or substituted with 1, 2, 3, 4, or 5 hydroxyl substituents,
with the proviso that no two hydroxyls are attached to the same carbon,
(v) heterocycle,
(w) hydroxyl,
(x) hydroxyalkyl wherein the hydroxyalkyl is unsubstituted or substituted with substitutients selected from the group consisting of aryl,
(y) loweralkyl wherein the loweralkyl is unsubstituted or substituted with substituents selected from the group consisting of
heterocycle,
hydroxyl,
with the proviso that no two hydroxyls are attached to the same carbon,
$-NR^{R3}R^{R3'}$, and
-P(O)(OR)(OR'),
(z) nitro,
(aa) -NRR',
(bb) oxo,
(cc) $-SO_2NR_{A'}R_{B'}$ wherein $R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of
hydrogen,
(aryl)oyl,
loweralkyl, and
heterocycle wherein the heterocycle is unsubstituted or substituted with 1, 2, or 3 substituents independently selected from the group consisting of loweralkyl,

(dd) sulfhydryl, and

(ee) thioalkoxy,

(5) cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1, 2, 3, 4 or 5 substituents selected from the group consisting of

(a) alkoxy,

(b) aryl,

(c) arylalkoxy

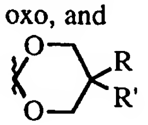
(d) aryloxy wherein the aryloxy is unsubstituted or substituted with 1, 2, 3, 4, or 5 substituents selected from the group consisting of halogen,

(e) loweralkyl,

(f) halogen,

(g) $NR^{R3}R^{R3'}$,

(h) oxo, and

(i) 

,

(6) cycloalkenyl wherein the cycloalkenyl is unsubstituted or substituted with 1, 2, 3 or 4 substituents independently selected from the group consisting of

(a) loweralkyl,

(b) alkoxy,

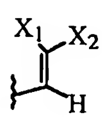
(c) halogen,

(d) aryl,

(e) aryloxy,

(f) alkanoyl, and

(g) $NR^{R3}R^{R3'}$,

(7) 

wherein X_1 and X_2 together are cycloalkyl wherein the cycloalkyl is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of aryl, and

(8) $-P(W)R^{R3}R^{R3'}$; and

R_4 is selected from the group consisting of

(1) hydrogen,
(2) loweralkyl,
(3) haloalkyl
(4) halogen,
(5) aryl,
(6) arylalkyl,
(7) heterocycle,
(8) (heterocyclic)alkyl
(9) alkoxy, and
(10) -NRR'; or

L_1, Z, and R_3 together are selected from the group consisting of

(1) aminoalkyl,
(1) haloalkyl,
(2) halogen,
(3) carboxaldehyde, and
(4) (carboxaldehyde)alkyl, and
(5) hydroxyalkyl,

with the proviso that when L_1, Z, and R_3 together are (1)-(5), R_1 is other than hydrogen.

In a further aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with a pharmaceutically acceptable carrier.

In yet another aspect of the present invention are disclosed pharmaceutical compositions which comprise a compound of formula I in combination with another chemotherapeutic agent and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is disclosed a method for inhibiting protein isoprenyl transferases (i.e., protein farnesyltransferase and/or geranylgeranyltransferase) in a human or lower mammal, comprising administering to the patient a therapeutically effective amount of a compound compound of formula I.

In yet another aspect of the present invention is disclosed a method for inhibiting post-translational modification of the oncogenic Ras protein by protein farnesyltransferase, protein geranylgeranyltransferase or both.

In yet another aspect of the present invention is disclosed a method for treatment of conditions mediated by farnesylated or geranylgeranylated proteins, for example, treatment of Ras associated tumors in humans and other mammals.

In yet another aspect of the present invention is disclosed a method for inhibiting or treating cancer in a human or lower mammal comprising administering to the patient a therapeutically effective amount of a compound of the invention alone or in combination with another chemotherapeutic agent

In yet another aspect of the present invention is disclosed a method for treating or preventing intimal hyperplasia associated with restenosis and atherosclerosis in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

The compounds of the invention can comprise asymmetrically substituted carbon atoms. As a result, all stereoisomers of the compounds of the invention are meant to be included in the invention, including racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30, which is hereby incorporated herein by reference.

Detailed Description

Definitions of Terms

As used herein the terms "Cys," "Glu," "Leu," "Lys,""Met," "nor-Leu," "nor-Val," "Phe," "Ser" and "Val" refer to cysteine, glutamine, leucine, lysine, methionine, norleucine, norvaline, phenylalanine, serine and valine in their L-, D- or DL forms. As used herein these amino acids are in their naturally occuring L- form.

As used herein, the term "carboxy protecting group" refers to a carboxylic acid protecting ester group employed to block or protect the carboxylic acid functionality while the reactions involving other functional sites of the compound are carried out. Carboxy protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis" pp. 152-186 (1981), which is hereby incorporated herein by reference. In addition, a carboxy protecting group can be used as a prodrug whereby the carboxy protecting group can be readily cleaved *in vivo* (for example by enzymatic hydrolysis) to release the biologically active parent. T. Higuchi and V. Stella provide a thorough discussion of the prodrug concept in "Pro-drugs as Novel Delivery Systems", Vol 14 of the A.C.S. Symposium Series, American Chemical Society (1975), which is hereby incorporated herein by reference. Such carboxy protecting groups are well known to those skilled in the art, having been extensively used in the protection of carboxyl groups in the penicillin and cephalosporin fields (as described in U.S. Pat. No. 3,840,556 and 3,719,667, the disclosures of which are hereby incorporated herein by reference). Examples of esters useful as prodrugs for compounds containing carboxyl groups can be found on pages 14-21

of "Bioreversible Carriers in Drug Design: Theory and Application", edited by E.B. Roche, Pergamon Press, New York (1987), which is hereby incorporated herein by reference. Representative carboxy protecting groups are C_1 to C_8 loweralkyl (e.g., methyl, ethyl or tertiary butyl and the like); arylalkyl, for example, phenethyl or benzyl and substituted derivatives thereof such as alkoxybenzyl or nitrobenzyl groups and the like; arylalkenyl, for example, phenylethenyl and the like; aryl and substituted derivatives thereof, for example, 5-indanyl and the like; dialkylaminoalkyl (e.g., dimethylaminoethyl and the like); alkanoyloxyalkyl groups such as acetoxymethyl, butyryloxymethyl, valeryloxymethyl, isobutyryloxymethyl, isovaleryloxymethyl, 1-(propionyloxy)-1-ethyl, 1-(pivaloyloxyl)-1-ethyl, 1-methyl-1-(propionyloxy)-1-ethyl, pivaloyloxymethyl, propionyloxymethyl and the like; cycloalkanoyloxyalkyl groups such as cyclopropylcarbonyloxymethyl, cyclobutylcarbonyloxymethyl, cyclopentylcarbonyloxymethyl, cyclohexylcarbonyloxymethyl and the like; aroyloxyalkyl, such as benzoyloxymethyl, benzoyloxyethyl and the like; arylalkylcarbonyloxyalkyl, such as benzylcarbonyloxymethyl, 2-benzylcarbonyloxyethyl and the like; alkoxycarbonylalkyl or cycloalkyloxycarbonylalkyl, such as methoxycarbonylmethyl, cyclohexyloxycarbonylmethyl, 1-methoxycarbonyl-1-ethyl, and the like; alkoxycarbonyloxyalkyl or cycloalkyloxycarbonyloxyalkyl, such as methoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, 1-ethoxycarbonyloxy-1-ethyl, 1-cyclohexyloxycarbonyloxy-1-ethyl and the like; aryloxycarbonyloxyalkyl, such as 2-(phenoxycarbonyloxy)ethyl, 2-(5-indanyloxycarbonyloxy)ethyl and the like; alkoxyalkylcarbonyloxyalkyl, such as 2-(1-methoxy-2-methylpropan-2-oyloxy)ethyl and like; arylalkyloxycarbonyloxyalkyl, such as 2-(benzyloxycarbonyloxy)ethyl and the like; arylalkenyloxycarbonyloxyalkyl, such as 2-(3-phenylpropen-2-yloxycarbonyloxy)ethyl and the like; alkoxycarbonylaminoalkyl, such as t-butyloxycarbonylaminomethyl and the like; alkylaminocarbonylaminoalkyl, such as methylaminocarbonylaminomethyl and the like; alkanoylaminoalkyl, such as acetylaminomethyl and the like; heterocycliccarbonyloxyalkyl, such as 4-methylpiperazinylcarbonyloxymethyl and the like; dialkylaminocarbonylalkyl, such as dimethylaminocarbonylmethyl, diethylaminocarbonylmethyl and the like; (5-(loweralkyl)-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-t-butyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like; and (5-phenyl-2-oxo-1,3-dioxolen-4-yl)alkyl, such as (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl and the like.

Preferred carboxy-protected compounds of the invention are compounds wherein the protected carboxy group is a loweralkyl, cycloalkyl or arylalkyl ester, for example, methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, sec-butyl ester, isobutyl ester, amyl ester, isoamyl ester, octyl ester, cyclohexyl ester, phenylethyl ester and the like or an

alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl or an arylalkylcarbonyloxyalkyl ester.

The term "N-protecting group" or "N-protected" as used herein refers to those groups intended to protect the N-terminus of an amino acid or peptide or to protect an amino group against undersirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, "Protective Groups In Organic Synthesis," (John Wiley & Sons, New York (1981)), which is hereby incorporated herein by reference. N-protecting groups comprise acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, a-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, p-toluenesulfonyl and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, a,a-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred N-protecting groups are formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz).

The term "alkanoyl" as used herein refers to $R_{29}C(O)$- wherein R_{29} is a loweralkyl group. The alkanoyl groups of this invention can be optionally substituted.

The term "alkanoylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{71}-NH- wherein R_{71} is an alkanoyl group. The alkanoylaminoalkyl groups of this invention can be optionally substituted.

The term "alkanoyloxy" as used herein refers to $R_{29}C(O)$-O- wherein R_{29} is a loweralkyl group. The alkanoyloxy groups of this invention can be optionally substituted.

The term "alkanoyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an alkanoyloxy group. The alkanoyloxyalkyl groups of this invention can be optionally substituted.

The term "alkenyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenyl include $-CH=CH_2$, $-CH_2CH=CH_2$, $-C(CH_3)=CH_2$, $-CH_2CH=CHCH_3$, and the like. The alkenyl groups of this invention can be optionally substituted.

The term "alkenylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 20 carbon atoms and also containing at least one carbon-carbon double bond. Examples of alkenylene include $-CH=CH-$, $-CH_2CH=CH-$, $-C(CH_3)=CH-$, $-CH_2CH=CHCH_2-$, and the like. The alkenylene groups of this invention can be optionally substituted.

The term "alkenyloxy" as used herein refers to an alkenyl group attached to the parent molecular group through an oxygen atom. The alkenyloxy groups of this invention can be optionally substituted.

The term "alkenyloxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkenyloxy group. The alkenyloxyalkyl groups of this invention can be optionally substituted.

The term "alkoxy" as used herein refers to $R_{30}O-$ wherein R_{30} is loweralkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like. The alkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to a loweralkyl group to which is attached an alkoxy group. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkoxy" as used herein refers to $R_{31}O-R_{32}O-$ wherein R_{31} is loweralkyl as defined above and R_{32} is an alkylene radical. Representative examples of alkoxyalkoxy groups include methoxymethoxy, ethoxymethoxy, t-butoxymethoxy and the like. The alkoxyalkoxy groups of this invention can be optionally substituted.

The term "alkoxyalkyl" as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxymethyl, methoxyethyl, isopropoxymethyl and the like. The alkoxyalkyl groups of this invention can be optionally substituted.

The term "alkoxyalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended $R_{66}-C(O)-O-$ wherein R_{66} is an alkoxyalkyl group.

The term "alkoxyarylalkyl" as used herein refers to a an arylalkyl group to which is attached an alkoxy group. The alkoxyarylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyl" as used herein refers to an alkoxy group as previously defined appended to the parent molecular moiety through a carbonyl group. Examples of

alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl and the like. The alkoxycarbonyl groups of this invention can be optionally substituted. The alkoxycarbonyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylalkyl" as used herein refers to an alkoxylcarbonyl group as previously defined appended to a loweralkyl radical. Examples of alkoxycarbonylalkyl include methoxycarbonylmethyl, 2-ethoxycarbonylethyl and the like. The alkoxycarbonylalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{69}-NH- wherein R_{69} is an alkoxycarbonyl group. The alkoxycarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkoxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{63}-O- wherein R_{63} is an alkoxycarbonyl group. The alkoxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "alkylamino" as used herein refers to R_{35}NH- wherein R_{35} is a loweralkyl group, for example, methylamino, ethylamino, butylamino, and the like. The alkylamino groups of this invention can be optionally substituted.

The term "alkylaminoalkyl" as used herein refers a loweralkyl radical to which is appended an alkylamino group. The alkylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylaminocarbonylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended R_{70}-C(O)-NH- wherein R_{70} is an alkylamino group. The alkylaminocarbonylaminoalkyl groups of this invention can be optionally substituted.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2-dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted.

The term "alkylsilyloxy" as used herein refers to a loweralkyl group to which is attached -OSi$R_{W'}R_{X'}R_{Y'}$ wherein $R_{W'}$, $R_{X'}$, and $R_{Y'}$ are selected from the group consisting of loweralkyl.

The term "alkylsulfinyl" as used herein refers to R_{33}S(O)- wherein R_{33} is a loweralkyl group. The alkylsulfinyl groups of this invention can be optionally substituted.

The term "alkylsulfinylalkyl" as used herein refers to an alkyl group to which is attached a alkylsulfinyl group. The alkylsulfinylalkyl groups of this invention can be optionally substituted.

The term "alkylsulfonyl" as used herein refers to $R_{34}S(O)_2$- wherein R_{34} is a loweralkyl group. The alkylsulfonyl groups of this invention can be optionally substituted.

The term "alkylsulfonylalkyl" as used herein refers to a loweralkyl radical to which is appended an alkylsulfonyl group. The alkylsulfonylalkyl groups of this invention can be optionally substituted.

The term alkylthioalkyl as used herein refers to a lower alkyl group as defined herein attached to the parent molecular moiety through a sulfur atom and an alkylene group. The alkylthioalkyl groups of this invention can be optionally substituted.

The term "alkynyl" as used herein refers to a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynyl include $-C{\equiv}CH$, $-CH_2C{\equiv}CH$, $-CH_2C{\equiv}CCH_3$, and the like. The alkynyl groups of this invention can be optionally substituted.

The term "alkynylene" as used herein refers to a divalent group derived from a straight or branched chain hydrocarbon containing from 2 to 10 carbon atoms and also containing at least one carbon-carbon triple bond. Examples of alkynylene include $-C{\equiv}C-$, $-CH_2C{\equiv}C-$, $-CH_2C{\equiv}CCH_2-$, and the like. The alkynylene groups of this invention can be optionally substituted.

The term "amino" as used herein refers to $-NH_2$.

The term "aminocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a carbonyl group. The aminocarbonyl groups of this invention can be optionally substituted.

The term "aminocarbonylalkyl" as used herein refers to an alkyl group to which is attached an aminocarbonyl group. The aminocarbonylalkyl groups of this invention can be optionally substituted.

The term "aminoalkyl" as used herein refers to a loweralkyl radical to which is appended an amino group. The aminoalkyl groups of this invention can be optionally substituted.

The term "aminothiocarbonyl" as used herein refers to an amino group attached to the parent molecular group through a thiocarbonylcarbonyl (C=S) group. The aminothiocarbonyl groups of this invention can be optionally substituted.

The term "aroyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an aroyloxy group (i.e., R_{61}-C(O)O- wherein R_{61} is an aryl group). The aroyloxyalkyl groups of this invention can be optionally substituted.

The term "aryl" as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, mercapto, sulfhydryl, nitro, cyano, carboxaldehyde, carboxy,

alkoxycarbonyl, haloalkyl-C(O)-NH-, haloalkenyl-C(O)-NH- and carboxamide. In addition, substituted aryl groups include tetrafluorophenyl and pentafluorophenyl.

The term "arylalkenyl" as used herein refers to an alkenyl radical to which is appended an aryl group. The arylalkenyl groups of this invention can be optionally substituted.

The term "arylalkenyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{68}-O-C(O)-O- wherein R_{68} is an arylalkenyl group. The arylalkenyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy group to which is attached an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyl" as used herein refers to a loweralkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl and the like. The arylalkyl groups of this invention can be optionally substituted.

The term "arylalkylcarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkylcarbonyloxy group (i.e., R_{62}C(O)O- wherein R_{62} is an arylalkyl group). The arylalkylcarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to an aryl group attached to the parent molecular group through an oxygen atom. The aryloxy groups of this invention can be optionally substituted.

The term "aryloxycarbonyl" as used herein refers to an aryloxy group attached to the parent molecular group through a carbonyl group. The aryloxycarbonyl groups of this invention can be optionally substituted.

The term "aryloyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The aryloyl groups of this invention can be optionally substituted.

The term "arylalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{67}-O-C(O)-O- wherein R_{67} is an arylalkyl group. The arylalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{65}-O- wherein R_{65} is an aryl group. The aryloxyalkyl groups of this invention can be optionally substituted.

The term "arylalkoxy" as used herein refers to an alkoxy radical to which is appended R_{65}-O- wherein R_{65} is an aryl group. The arylalkoxy groups of this invention can be optionally substituted.

The term "arylalkyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended an arylalkoxy group. The arylalkyloxyalkyl groups of this invention can be optionally substituted.

The term "aryloxy" as used herein refers to R_{65}-O- wherein R_{65} is an aryl group. The aryloxy groups of this invention can be optionally substituted. The aryloxy groups of this invention can be optionally substituted.

The term "(aryl)oyl" as used herein refers to an aryl group attached to the parent molecular group through a carbonyl group. The (aryl)oyl groups of this invention can be optionally substituted.

The term "aryloxythioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{75}-S- wherein R_{75} is an aryloxyalkyl group. The aryloxythioalkoxyalkyl groups of this invention can be optionally substituted.

The term "aryloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{65}-O-C(O)-O- wherein R_{65} is an aryl group. The aryloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "arylsulfonyl" as used herein refers to $R_{36}S(O)_2$- wherein R_{36} is an aryl group. The arylsulfonyl groups of this invention can be optionally substituted.

The term "arylsulfonyloxy" as used herein refers to $R_{37}S(O)_2O$- wherein R_{37} is an aryl group. The arylsulfonyloxy groups of this invention can be optionally substituted.

The term "carboxy" as used herein refers to -COOH.

The term "carboxyalkyl" as used herein refers to a loweralkyl radical to which is appended a carboxy (-COOH) group. The carboxyalkyl groups of this invention can be optionally substituted.

The term "cyanoalkyl" as used herein used herein refers to a loweralkyl radical to which is appended a cyano (-CN) group. The cyanoalkyl groups of this invention can be optionally substituted.

The term "carboxaldehyde" as used herein used herein refers to -CHO.

The term "(carboxaldehyde)alkyl" as used herein used herein refers to a carboxaldehyde group attached to a loweralkyl group. The (carboxaldehyde)alkyl groups of this invention can be optionally substituted.

The terms "cycloalkanoyl" and "(cycloalkyl)oyl" refer to a cycloalkyl group attached to the parent molecular group through a carbonyl group. The cycloalkanoyl and (cycloalkyl)oyl groups of this invention can be optionally substituted.

The term "cycloalkanoylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkanoyl group (i.e., R_{60}-C(O)- wherein R_{60} is a cycloalkyl group). The cycloalkanoylalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a cycloalkyl group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

The term "cycloalkenyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms and containing a carbon-carbon double bond including, but not limited to, cyclopentenyl, cyclohexenyl and the like. The cycloalkenyl groups of this invention can be optionally substituted.

The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through an oxygen atom. The cycloalkoxy groups of this invention can be optionally substituted.

The term "cycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a cycloalkoxy group. The cycloalkoxyalkyl groups of this invention can be optionally substituted.

The term "cycloalkoxycarbonyl" as used herein refers to a cycloalkoxy group attached to the parent molecular group through a carbonyl group. The cycloalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkyl" as used herein refers to an alicyclic group comprising from 3 to 10 carbon atoms including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, adamantyl and the like. The cycloalkyl groups of this invention can be optionally substituted. The cycloalkyl groups of this invention can be optionally substituted.

The term "cycloalkylaminocarbonyl" as used herein refers to $NHR_{60'}C(O)$- wherein $R_{60'}$ is a cycloalkyl group. The cycloalkylaminocarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylaminothiocarbonyl" as used herein refers to $NHR_{60'}C(S)$- wherein $R_{60'}$ is defined above. The cycloalkylaminothiocarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxy" as used herein refers to an alkoxy radical to which is appended a cycloalkyl group. The cycloalkylalkoxy groups of this invention can be optionally substituted.

The term "cycloalkylalkoxyalkyl" as used herein refers to an alkyl radical to which is appended a cycloalkylalkoxy group. The cycloalkylalkoxyalkyl groups of this invention can be optionally substituted.

The term "cycloalkylalkoxycarbonyl" as used herein refers to a cycloalkylalkoxy radical attached to the parent molecular group through a carbonyl group. The cycloalkylalkoxycarbonyl groups of this invention can be optionally substituted.

The term "cycloalkylalkyl" as used herein refers to a loweralkyl radical to which is appended a cycloalkyl group. Representative examples of cycloalkylalkyl include cyclopropylmethyl, cyclohexylmethyl, 2-(cyclopropyl)ethyl, adamantylmethyl and the like. The cycloalkylalkyl groups of this invention can be optionally substituted.

The term "cycloalkyloxycarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{64}-O-C(O)-O- wherein R_{64} is a cycloalkyl group. The cycloalkyloxycarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "dialkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two alkoxy groups. The dialkoxyalkyl groups of this invention can be optionally substituted.

The term "dialkylamino" as used herein refers to $R_{38}R_{39}N$- wherein R_{38} and R_{39} are independently selected from loweralkyl, for example dimethylamino, diethylamino, methyl propylamino, and the like. The dialkylamino groups of this invention can be optionally substituted.

The term "dialkylaminoalkyl" as used herein refers to a loweralkyl radical to which is appended a dialkylamino group. The dialkylaminoalkyl groups of this invention can be optionally substituted.

The term "dialkyaminocarbonylalkyl" as used herein refers to a loweralkyl radical to which is appended R_{73}-C(O)- wherein R_{73} is a dialkylamino group. The dialkyaminocarbonylalkyl groups of this invention can be optionally substituted.

The term "dioxoalkyl" as used herein refers to a loweralkyl radical which is substituted with two oxo (=O) groups. The dioxoalkyl groups of this invention can be optionally substituted.

The term "dithioalkoxyalkyl" as used herein refers to a loweralkyl radical to which is appended two thioalkoxy groups. The dithioalkoxyalkyl groups of this invention can be optionally substituted.

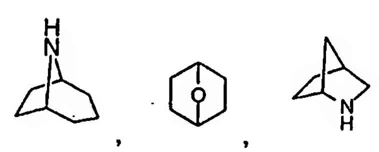
The term "halogen" or "halo" as used herein refers to I, Br, Cl or F.

The term "haloalkenyl" as used herein refers to an alkenyl radical, as defined above, bearing at least one halogen substituent. The haloalkenyl groups of this invention can be optionally substituted.

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl or trifluoromethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorides.

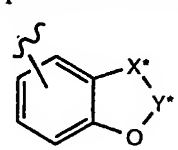
The term "heterocyclic ring" or "heterocyclic" or "heterocycle" as used herein refers to a 5-, 6- or 7-membered ring containing one, two or three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur or a 5-membered ring

containing 4 nitrogen atoms; and includes a 5-, 6- or 7-membered ring containing one, two or three nitrogen atoms; one oxygen atom; one sulfur atom; one nitrogen and one sulfur atom; one nitrogen and one oxygen atom; two oxygen atoms in non-adjacent positions; one oxygen and one sulfur atom in non-adjacent positions; two sulfur atoms in non-adjacent positions; two sulfur atoms in adjacent positions and one nitrogen atom; two adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one sulfur atom; two non-adjacent nitrogen atoms and one oxygen atom. The 5-membered ring has 0-2 double bonds and the 6- and 7-membered rings have 0-3 double bonds. The term "heterocyclic" also includes bicyclic, tricyclic and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from the group consisting of an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring and another monocyclic heterocyclic ring (for example, indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl or benzothienyl and the like). Heterocyclics include: pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, pyrimidyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranyl and benzothienyl. Heterocyclics also include bridged bicyclic groups wherein a monocyclic heterocyclic group is bridged by an alkylene group, for example,



and the like.

Heterocyclics also include compounds of the formula



wherein X* is -CH_2-, -CH_2O- or -O- and Y* is -C(O)- or -$(C(R'')_2)_v$ - wherein R" is hydrogen or C_1-C_4-alkyl and v is 1, 2 or 3 such as 1,3-benzodioxolyl, 1,4-benzodioxanyl and the like.

Heterocyclics can be unsubstituted or substituted with one, two, three, four or five substituents independently selected from the group consisting of a) hydroxy, b) -SH, c) halo, d) oxo (=O), e) thioxo (=S), f) amino,g) -NHOH, h) alkylamino, i) dialkylamino, j) alkoxy, k) alkoxyalkoxy, l) haloalkyl, m) hydroxyalkyl, n) alkoxyalkyl, o) cycloalkyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, p) cycloalkenyl which is unsubstituted or substituted with one, two, three or four loweralkyl groups, q) alkenyl, r) alkynyl, s) aryl, t) arylalkyl, u) -COOH, v) $-SO_3H$, w) loweralkyl, x) alkoxycarbonyl, y) $-C(O)NH_2$, z) $-C(S)NH_2$, aa) $-C(=N-OH)NH_2$, bb) aryl-L_{16}-C(O)- wherein L_{16} is an alkenylene radical, cc) -S-L_{17}-C(O)OR_{40} wherein L_{17} is an alkylene radical which is unsubstituted or substituted with one or two substitutents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHN$R_{41}R_{42}$ wherein R_{41} is hydrogen or loweralkyl and R_{42} is loweralkyl) and R_{40} is hydrogen or a carboxy-protecting group, dd) -S-L_{18}-C(O)N$R_{43}R_{44}$ wherein L_{18} is an alkylene radical which is unsubstituted or substituted with one or two substitutents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHN$R_{41}R_{42}$ wherein R_{41} is hydrogen or loweralkyl and R_{43} and R_{44} are independently selected from the group consisting of hydrogen, loweralkyl and aryl, ee) -S-L_{19}-CN wherein L_{19} is an alkylene radical, ff) -S-L_{20}-R_{45} wherein L_{20} is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with oxo (=O) and R_{45} is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, gg) -O-L_{21}-R_{46} wherein L_{21} is absent or is an alkylene radical or an alkenylene radical or an alkynylene radical wherein the alkylene, alkenylene or alkynylene radical is unsubstituted or substituted with one or two substitutents independently selected from the group consisting of alkanoyl, oxo (=O) or methinylamino (=CHN$R_{41}R_{42}$ wherein R_{41} is hydrogen or loweralkyl and R_{46} is hydrogen, aryl, arylalkyl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, hh) $-O-S(O)_2-R_{47}$ wherein R_{47} is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ii) $-S(O)_2-NH-R_{48}$ wherein R_{48} is aryl, arylalkyl, heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or

substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, jj) alkylsulfinyl, kk) alkylsulfonyl, ll) arylsulfonyl, mm) arylsulfonyloxy, nn) -C(=NOR$_{49}$)C(O)OR$_{50}$ wherein R$_{49}$ is hydrogen or loweralkyl and R$_{50}$ is hydrogen or a carboxy-protecting group, oo) alkoxycarbonylalkyl, pp) carboxyalkyl, qq) cyanoalkyl, rr) alkylaminoalkyl, ss) N-protected alkylaminoalkyl, tt) dialkylaminoalkyl, uu) dioxoalkyl, vv) loweralkyl-C(O)-, ww) loweralkyl-C(S)-, xx) aryl-C(O)-, yy) aryl-C(S)-, zz) loweralkyl-C(O)-O-, aaa) loweralkyl-S-C(S)- bbb) N-protected amino, ccc) aminoalkyl-C(O)-, ddd) N-protected aminoalkyl-C(O)- eee) aminoalkyl-C(S)-, fff) N-protected aminoalkyl-C(S)-, ggg) aminoalkyl, hhh) N-protected aminoalkyl, iii) formyl, jjj) cyano, kkk) nitro, lll) spiroalkyl, mmm) oxoalkyloxy, nnn) R$_{53}$-L$_{22}$-, wherein L$_{22}$ is alkenylene or alkynylene and R$_{53}$ is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, ooo) aryl-NH-C(O)-, ppp) R$_{54}$-N=N- wherein R$_{54}$ is aryl or heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, qqq) =N-R$_{55}$ wherein R$_{55}$ is hydrogen, aryl, heterocyclic, -S(O)$_2$-aryl or -S(O)$_2$-heterocyclic wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, rrr) diarylalkyl-N=N-, sss) aryl-N(R$_{56}$)- or arylalkyl-N(R$_{56}$)- wherein R$_{56}$ is hydrogen or an N-protecting group, ttt) aryl-sulfonylalkyl, uuu) heterocyclicsulfonylalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, vvv) =C(CN)(C(O)NH$_2$), www) =C(CN)(C(O)O-loweralkyl), xxx) heterocyclic or heterocyclicalkyl wherein the heterocyclic is unsubstituted or substituted with one, two or three substituents independently selected from the group consisting of loweralkyl, hydroxy, hydroxyalkyl, halo, nitro, oxo (=O), amino, N-protected amino, alkoxy, thioalkoxy and haloalkyl, yyy) hydroxythioalkoxy, zzz) aryloxyalkyl, aaaa) aryloxyalkylthioalkoxy, bbbb) dialkoxyalkyl, cccc) dithioalkoxyalkyl, dddd) arylalkyl-NH-L$_{23}$- wherein L$_{23}$ is an alkylene group, eeee) heterocyclicalkyl-NH-L$_{24}$- wherein L$_{24}$ is an alkylene group, ffff) aryl-S(O)$_2$-NH-L$_{25}$- wherein L$_{25}$ is an alkylene group, gggg) heterocyclic-S(O)$_2$-NH-L$_{26}$- wherein L$_{26}$ is an alkylene group, hhhh) aryl-C(O)-NH-L$_{27}$- wherein L$_{27}$ is an alkylene group and iiii) heterocyclic-C(O)-NH-L$_{28}$-

wherein L_{28} is an alkylene group, jjjj) $Ryy(CH2)_n$-X-Y-Z-$(CH2)_m$ wherein Ryy is cycloalkyl, aryl and loweralkyl, n amd m are independently 0-2, Z is O or absent, Y is absent, CH_2, CHOH or C(O), with the proviso that when X is O, Z is absent and with the proviso that when Z is O, X is absent and with the proviso that when Y is CHOH, X and Z are absent.

The term "(heterocyclic)alkoxy" as used herein refers to an alkoxy group to which is attached a heterocycle. The (heterocyclic)alkoxy groups of this invention can be optionally substituted.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group as defined above appended to a loweralkyl radical as defined above. Examples of heterocyclic alkyl include 2-pyridylmethyl, 4-pyridylmethyl, 4-quinolinylmethyl and the like. The (heterocyclic)alkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)oxy" as used herein refers to a heterocycle connected to the parent molecular group through an oxygen atom. The (heterocyclic)oxy groups of this invention can be optionally substituted.

The term "(heterocyclic)oxyalkyl" as used herein refers to a loweralkyl group to which is attached a (heterocyclic)oxy group. The (heterocyclic)oxyalkyl groups of this invention can be optionally substituted.

The term "(heterocyclic)alkoxyalkyl" as used herein refers to an alkoxyalkyl group to which is attached a heterocycle. The (heterocyclic)alkoxyalkyl groups of this invention can be optionally substituted.

The term "heterocycliccarbonyloxyalkyl" as used herein refers to a loweralkyl radical to which is appended R_{72}-C(O)-O- wherein R_{72} is a heterocyclic group. The heterocycliccarbonyloxyalkyl groups of this invention can be optionally substituted.

The term "hydroxy" as used herein refers to -OH.

The term "hydroxyalkyl" as used herein refers to a loweralkyl radical to which is appended an hydroxy group. The hydroxyalkyl groups of this invention can be optionally substituted.

The term "hydroxyarylalkyl" as used herein refers to a arylalkyl group to which is appended a hydroxy group. The hydroxyarylalkyl groups of this invention can be optionally substituted.

The term "hydroxythioalkoxy" as used herein refers to R_{51}S- wherein R_{51} is a hydroxyalkyl group. The hydroxythioalkoxy groups of this invention can be optionally substituted.

The term "loweralkyl" as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon atoms, including methyl, ethyl, propyl, isopropyl, n-

butyl, t-butyl, neopentyl and the like. The loweralkyl groups of this invention can be optionally substituted.

The term "N-protected alkylaminoalkyl" as used herein refers to an alkylaminoalkyl group wherein the nitrogen is N-protected. The N-protected alkylaminoalkyl groups of this invention can be optionally substituted.

The term "nitro" as used herein refers to $-NO_2$.

The term "oxo" as used herein refers to (=O).

The term "oxoalkyloxy" as used herein refers to an alkoxy radical wherein the loweralkyl moiety is substituted with an oxo (=O) group. The oxoalkyloxy groups of this invention can be optionally substituted.

The term "oxyamino(alkyl)carbonylalkyl" as used herein refers to a -O-NR-C(O)-R' group wherein R and R' are loweralkyl.

The term "oxyamino(arylalkyl)carbonylalkyl" as used herein refers to a -O-NR^{R_3}-C(O)-R group wherein R^{R_3} is arylalkyl and R is loweralkyl.

The term "oxyaminocarbonylalkyl" as used herein refers to -O-NH-C(O)-R group wherein R is loweralkyl.

The term "spiroalkyl" as used herein refers to an alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group. The spiroalkyl groups of this invention can be optionally substituted.

The term "sulfhydryl" as used herein refers to -SH.

The term "sulfhydrylalkyl" as used herein refers to a loweralkyl group to which is attached a sulfhydryl group. The sulfhydrylalkyl groups of this invention can be optionally substituted.

The term "thioalkoxy" as used herein refers to $R_{52}S$- wherein R_{52} is loweralkyl. Examples of thioalkoxy include, but are not limited to, methylthio, ethylthio and the like. The thioalkoxy groups of this invention can be optionally substituted.

The term "thioalkoxyalkyl" as used herein refers to a thioalkoxy group as previously defined appended to a loweralkyl group as previously defined. Examples of thioalkoxyalkyl include thiomethoxymethyl, 2-thiomethoxyethyl and the like. The thioalkoxyalkyl groups of this invention can be optionally substituted.

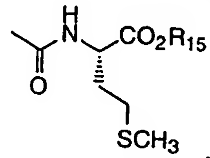
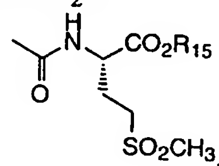
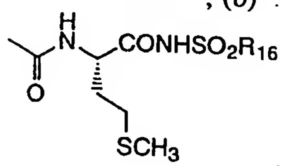
The term "thiocycloalkoxy" as used herein refers to a cycloalkyl group attached to the parent molecular group through a sulfur atom. The thiocycloalkoxy groups of this invention can be optionally substituted.

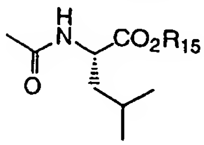
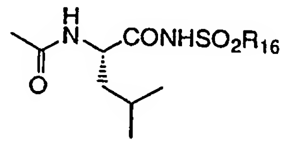
The term "thiocycloalkoxyalkyl" as used herein refers to a loweralkyl group to which is attached a thiocycloalkoxy group. The thiocycloalkoxyalkyl groups of this invention can be optionally substituted.

Preferred embodiments

Preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is -C(O)NH-CH(R_{14})-C(O)OR_{15} or -C(O)NH-CH(R_{14})-C(O)NHSO_2R_{16} wherein L_2, R_{14} R_{15} and R_{16} are defined above.

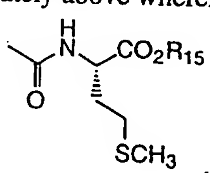
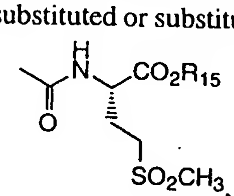
More preferred compounds of the invention are compounds of formula I wherein R_1 is unsubstituted or substituted phenyl and R_2 is

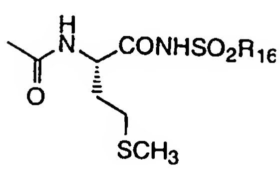
(a) , (b) , (c) ,

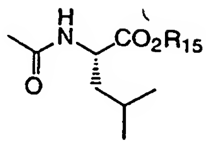
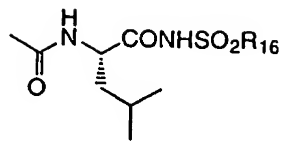
(d)  or (e) .

Still more preferred compounds have formula I wherein R_3 is selected from the group consisting of (a) pyridyl, (b) imidazolyl, and (c) furyl wherein the pyridyl, imidazolyl, or furyl group may be substituted with 1, 2 or 3 substituents selected from the group consisting of aryl, loweralkyl, halo, nitro, haloalkyl, hydroxy, hydroxyalkyl, amino, N-protected amino, alkoxy, and thioalkoxy.

Still more preferred compounds of the invention have the structure defined immediately above wherein R_1 is unsubstituted or substituted phenyl and R_2 is

(a) , (b) ,

(c) ,

(d)  , or (e) 

The most preferred compounds have the structure defined immediately above wherein R_3 is unsubstituted or substituted pyridyl or imidazolyl.

<u>Protein Farnesyltransferase Inhibition</u>

The ability of the compounds of the invention to inhibit protein farnesyltransferase or protein geranylgeranyltransferase can be measured according to the method of Moores, et al., J. Biol. Chem. 266: 14603 (1991) or the method of Vogt, et al., J. Biol. Chem. 270:660-664 (1995). In addition, procedures for determination of the inhibition of farnesylation of the oncogene protein Ras are described by Goldstein, et al., J. Biol. Chem., 266:15575-15578 (1991) and by Singh in United States Patent No. 5,245,061.

In addition, *in vitro* inhibition of protein farnesyltransferase may be measured by the following procedure. Rat brain protein farnesyltransferase activity is measured using an Amersham Life Science commercial scintillation proximity assay kit and substituting a biotin-K Ras B fragment (biotin-Lys-Lys-Ser-Lys-Thr-Lys-Cys-Val-Ile-Met-CO_2H), 0.1 m<u>M</u> final concentration, for the biotin-lamin substrate provided by Amersham. The enzyme is purified according to Reiss, Y., et al., Cell, 62: 81-88 (1990), utilizing steps one through three. The specific activity of the enzyme is approximately 10 nmol substrate farnesylated/mg enzyme/hour. The percent inhibition of the farnesylation caused by the compounds of the invention (at 10×10^{-6} <u>M</u>) compared to an uninhibited control sample is evaluated in the same Amersham test system.

The % inhibition of protein farnesyltransferase was determined for representative compounds of the invention. The results are summarized in Table 1.

Tables 1-5

In Vitro Potencies of Representative Compounds

Table 1. Inhibition of farnesyltransferase

Example	% inhibition at $1X10^{-5}$ M	Example	% inhibition at $1X10^{-5}$ M
200	93	674	40
350	53	676	76
351	82	678	73
352	52	680	58
353	62	683	57
354	47	684	48
355	43	685	55
356	58	686	48
357	56	687	78
358	45	688	71
359	36	689	73
360	88	690	61
361	97	692	74
362	83	699	74
363	96	700	68
364	69	701	64
365	97	702	79
366	83	704	67
367	81	705	72
368	71	706	53
369	87	707	66
370	86	708	76
371	66	709	55
372	69	710	45
373	76	711	46
374	61	712	69
375	68	713	40
376	80	714	56
377	71	715	67
378	54	717	75

380	45	718	40
381	79	750	44
382	> 50	752	58
383	> 50	753	55
387	> 50	754	40
388	> 50	755	44
390	> 50	756	47
639	44	757	58
659	55	758	46
663	43	759	49
664	75	952	> 50
669	52	955	50
670	78	974	> 50
672	48		

Table 2. Inhibition of farnesyltransferase

Example	% inhibition at $1X10^{-6}$ M	Example	% inhibition at $1X10^{-6}$ M
157	92	583	98
158	2	587	97
159	84	595	97
160	30	607	96
161	54	610	94
162	12	613	97
163	18	617	99
164	92	620	98
165	74	626	61
166	97	627	85
167	98	632	43
168	92	633	32
183	98	636	72
184	36	641	34
185	93	642	48
186	86	644	54
187	68	386	> 50
188	40	399	> 50
189	88	403	99
190	4	404	98
191	28	405	98
192	95	406	95
193	4	407	98
196	43	435	96
197	1	451	85
201	63	452	96
202	31	453	90
203	76	456	81
204	98	457	92
205	98	460	88
206	67	463	91
207	98	465	92
208	98	466	93

209	74	467	97
210	5	468	96
211	98	469	92
212	12	470	95
213	98	471	94
214	97	472	97
215	82	473	96
216	67	474	92
217	99	475	21
218	89	476	91
219	56	477	98
220	92	478	98
221	55	479	95
222	41	480	87
223	63	481	95
224	41	488	41
225	93	494	96
226	23	495	95
227	94	496	93
228	39	497	94
231	50	498	98
233	65	499	98
234	4	500	98
235	95	501	84
237	98	502	24
238	22	503	57
239	97	504	90
240	98	505	72
241	41	507	95
242	99	507	96
243	23	508	95
244	21	509	77
245	50	510	84
248	79	512	94
249	77	513	96
250	96	514	94

252	98	515	72
253	99	516	95
254	96	525	99
255	98	528	99
256	98	529	99
257	98	530	94
258	98	537	97
259	98	540	40
260	98	645	37
261	98	646	58
262	98	649	86
263	99	650	68
264	98	651	33
265	98	652	41
266	97	653	62
267	96	655	35
268	98	657	32
269	98	658	73
270	98	661	45
271	84	662	68
272	96	665	55
273	96	666	82
274	94	667	83
276	98	671	36
277	98	673	59
278	99	677	37
279	99	682	31
280	98	691	34
281	98	693	53
282	76	694	45
283	98	696	57
284	83	697	39
286	84	703	40
287	24	716	69
288	22	719	90
289	23	720	70

290	74	721	83
291	23	722	96
292	36	723	87
294	98	724	87
295	94	725	78
296	89	726	81
297	65	727	95
298	43	744	84
299	94	749	84
300	22	751	32
301	98	764	88
302	31	765	76
304	99	768	67
305	99	771	72
306	99	772	79
307	82	773	41
308	62	774	48
309	98	775	32
310	98	776	36
311	97	777	83
313	94	782	96
314	97	786	34
315	93	787	70
316	63	788	44
317	54	789	86
318	98	790	88
319	98	791	53
320	93	792	88
321	90	793	94
322	98	794	92
323	98	796	35
324	98	797	35
325	99	806	72
326	91	807	90
327	97	808	88
328	96	809	78

329	98
330	98
331	98
332	26
333	99
334	93
343	72
344	95
345	91
346	98
347	95
348	66
349	99
379	21
541	37
542	67
544	35
545	88
546	97
547	91
550	96
	78
728	
552	88
553	92
554	96
555	85
556	99
557	93
560	91
561	91
564	98
565	94
566	98
568	93

810	89
812	94
813	95
816	87
824	90
831	92
832	80
834	55
835	96
844	92
846	85
850	90
862	95
866	62
867	71
868	89
872	74
878	95
879	95
886	35
889	95
902	85
903	78
908	88
910	42
911	65
918	97
923	78
924	77
925	87
926	69
936	
	69
937	95
962	> 50

569	91	964	> 50
572	91	979	26
575	70	982	64
576	88	987	93
577	94	988	92
582	99	989	88

Table 3. Inhibition of farnesyltransferase

Example	% inhibition at 1X10^{-7} M	Example	% inhibition at 1X10^{-7} M
434	93	623	96
436	89	729	73
437	89	730	96
438	90	731	65
439	80	732	84
440	92	733	60
441	91	734	49
442	88	735	96
443	97	736	96
444	95	737	95
445	94	738	54
446	91	739	83
447	91	740	94
448	92	741	89
449	91	742	87
450	96	743	51
455	83	745	93
458	87	746	84
459	92	747	68
461	93	748	56
462	91	769	90
464	86	770	91
482	96	781	91
483	95	785	96
484	97	795	87
485	96	798	95
486	97	799	96
487	81	800	74
489	86	801	87
490	70	802	88
491	94	811	85
492	95	814	81
493	51	815	71

511	82	817	60
519	89	818	78
520	97	822	93
521	94	823	75
522	93	825	79
523	97	839	63
524	99	849	66
526	96	854	78
527	97	855	92
531	74	856	97
532	88	857	92
533	91	859	86
534	84	861	65
535	89	863	72
536	79	864	84
539	89	865	95
548	86	869	92
549	98	874	90
551	93	875	92
558	87	876	92
559	96	891	94
562	95	893	87
563	95	894	89
570	92	895	92
571	88	896	96
573	72	900	95
574	81	906	88
578	90	912	85
579	92	913	89
580	90	914	91
581	96	917	78
584	96	919	91
585	96	921	82
589	91	929	81
590	95	931	98
592	93	933	91

593	86	935	72
594	95	940	92
597	75	941	90
600	93	945	80
601	92	947	79
602	97	948	75
604	86	949	57
609	95	950	71
611	95	951	71
615	94	959	> 50
616	95	983	66
618	89	984	86
621	98	990	84
622	95	993	90

Table 4. Inhibition of farnesyltransferase

Example	% inhibition at 1X10-8 M	Example	% inhibition at 1X10-8 M
384	91	851	82
397	50	852	79
398	> 50	853	85
400	98	858	60
401	66	860	85
408	> 95	870	91
409	84	871	94
410	94	873	97
517	92	877	68
518	90	880	95
567	69	881	69
586	90	882	79
588	68	883	91
591	82	884	94
599	86	885	95
603	94	887	92
605	68	888	86
606	93	892	59
608	91	897	76
612	96	898	82
614	92	899	88
619	95	901	84
760	95	904	85
762	84	905	86
763	92	907	79
766	95	909	79
767	97	916	96
779	70	920	96
780	71	922	96
803	95	927	74
804	95	928	84
805	96	930	66
819	76	932	60

820	66	934	71
821	75	938	61
826	92	939	72
827	77	942	58
828	87	943	79
829	92	944	88
833	78	946	52
836	95	954	> 50
837	91	958	> 50
838	92	960	> 50
840	73	985	89
841	93	986	95
842	88	991	69
843	96	992	93
845	85	994	83
847	85	995	92
848	87	996	80

Table 5. Inhibition of geranylgeranyltransferase I.

Example	Activity
387	> 50% inhibition at 1 X 10^{-6} M
388	> 50% inhibition at 1 X 10^{-7} M
389	> 50% inhibition at 1 X 10^{-6} M
390	> 50% inhibition at 1 X 10^{-5} M
392	> 50% inhibition at 1 X 10^{-5} M
399	> 50% inhibition at 1 X 10^{-6} M
953	> 50% inhibition at 1 X 10^{-6} M
955	> 50% inhibition at 1 X 10^{-7} M
962	> 50% inhibition at 1 X 10^{-7} M
964	> 50% inhibition at 1 X 10^{-6} M
966	> 50% inhibition at 1 X 10^{-6} M
967	> 50% inhibition at 1 X 10^{-6} M
969	> 50% inhibition at 1 X 10^{-5} M
974	> 50% inhibition at 1 X 10^{-5} M

Table 6. Inhibition of farnesyltransferase at concentrations of 10 mM and 1 mM unless specified as * (0.1 mM) or ** (0.01 mM)

Example	% inhibition 10 mM	% inhibition 1 mM	Example	% inhibition 10 mM	% inhibition 1 mM
997		91**	1199		71
998		79**	1200		97*
999		90	1201		73*
1000		82*	1202		96**
1001		92**	1203		84*
1002		82**	1204		93*
1003		92*	1205		55**
1004		92**	1206		63**
1005		95**	1207		91*
1006		95**	1208		89*
1007		85**	1209		87*
1008		95**	1210		64**
1009		86**	1211		94
1010		90*	1212		86*

1011		92**	1213		79**
1012		88*	1214		92**
1013		80*	1215		17
1014		91	1216		88**
1015		59*	1217		87*
1016		92*	1218		54**
1017		51*	1219		85**
1018		97	1220		
1019		70	1221		82**
1020		39	1222		89*
1021		93*	1223		91**
1022		91**	1224		88*
1023		89**	1225		92**
1024		89**	1226		69**
1025		91**	1227		91
1026		74**	1228		88*
1027		81**	1229		66**
1028		92**	1230		77**
1029		82**	1231		93*
1030		92**	1232		68**
1031		90**	1233		77**
1032		93**	1234		71**
1033		76**	1235		86**
1034		77	1236		83**
1035		76	1237		89**
1036		79	1238		91**
1037		88	1239		85*
1038		57	1240		64**
1039		89**	1241		74*
1040		90**	1242		75*
1041		48	1243		95*
1042		88	1244		84
1043		90*	1245		92
1044		76*	1246		82

1045		86*	1247		95*
1046		93	1248		88
1047		95	1249		89
1048		78**	1250		79**
1049		93**	1251		91**
1050		62**	1252		84*
1051		79**	1253		76*
1052		91**	1254		67
1053		60**	1255		82*
1054		89**	1256		95*
1055		85**	1257		93**
1056		75**	1258		97**
1057		82*	1259		89**
1058		89	1260		90**
1059		92*	1261		94
1060		42	1262		95
1061		88*	1263		85*
1062		93	1264		83**
1063		92**	1265		90
1064		95**	1266		85*
1065		78*	1267		96
1066		73**	1268		95*
1067		93*	1269		84**
1068		79**	1270		91**
1069		74*	1271		78**
1070		93**	1272		73**
1071		95*	1273		94*
1072		82*	1274		89*
1073		93**	1275		86**
1074		82	1276		88**
1075		90**	1277		90**
1076		69**	1278		68
1077		93**	1279		87**
1078		86*	1280		78**

1079		90	1281		81*
1080		87	1282		69*
1081		61	1283		74*
1082		84*	1284		86
1083		88	1285		94
1084		76**	1286		85**
1085		93*	1287		95**
1086		87*	1288		69*
1087		76*	1289		93
1088		73*	1290		80
1089		86*	1291		
1090		81**	1292		
1091		87*	1293		
1092		74**	1294		
1093		95**	1295		
1094		96**	1296		
1095		76*	1297		
1096		86*	1298		97**
1097		80**	1299		96**
1098		60*	1300		97*
1099		87**	1301		97*
1100		82**	1302		93**
1101		86*	1303		91**
1102		84**	1304		90**
1103		92*	1305		91**
1104		89**	1306		85**
1105		91**	1307		85**
1106		67**	1308		91**
1107		88**	1309		96*
1108		95**	1310		90**
1109		74**	1311		95**
1110			1312		91**
1111		63**	1313		91**
1112		62	1314		96*

1113		55	1315		86*
1114		83**	1316		78*
1115		94*	1317	99	96
1116		91**	1318		
1117		92*	1319		79**
1118		86*	1320		79
1119		84**	1321		
1120		93	1322		
1121		72*	1323		
1122		92**	1324		
1123		90*	1325		
1124		90*	1326		
1125		92*	1327		
1126		87	1328		
1127		90*	1329		
1128		86*	1330		
1129		92**	1331		
1130		88**	1332		92**
1131		96**	1333		95*
1132		97*	1334		72**
1133		75*	1335		90*
1134		95**	1336		74
1135		88*	1337		83**
1136		91	1338		65*
1137		83**	1339		
1138		65*	1340		77*
1139		92*	1341		89
1140		77**	1342		
1141		80*	1343		88
1142		84**	1344		93**
1143		92*	1345		94**
1144		76*	1346		94*
1145		83*	1347		81**
1146		61**	1348		78**

1147		93*	1349		92**
1148		79**	1350		
1149		94*	1351		
1150		92*	1352		
1151		91*	1353		
1152		96*	1354		38
1153		89*	1355		46
1154		93*	1356		80
1155		91*	1357		78
1156		87	1358		
1157		66**	1359		
1158	75		1360		98**
1159		72*	1361		96*
1160		83*	1362		83**
1161		87*	1363		88**
1162		84*	1364		
1163		73**	1365		
1164		94	1366		79*
1165		84*	1367		93*
1166		74**	1368		92**
1167		91*	1369		94*
1168		88*	1370		86**
1169		77	1371		94*
1170		74*	1372		95**
1171		74**	1373		95**
1172		38*	1374		93**
1173		89**	1375		80**
1174		79**	1376		86**
1175		96	1377		95*
1176		97*	1378		68
1177		19	1379		41
1178		88**	1380		87**
1179		85*	1381		65**
1180		93*	1382		86**

1181		82*
1182		92**
1183		79**
1184		84**
1185		85**
1186		93**
1187		93**
1188		93**
1189		74**
1190		95**
1191		85**
1192		91*
1193		95**
1194		78**
1195		94*
1196		87*
1197		85*
1198		86*
1383		88*
1384		69**
1385		93*
1386		88*
1387		82**
1392		93*
1397		87**
1398		81*
1399		94
1400		95

* % inhibition at 0.1 μM

** % inhibition at 0.01 μM

Additional methods for the measurement of *in vitro* inhibition of protein prenylation (i.e., inhibition of farnesyltransferase or geranygeranyltransferase) are described below.

Assays are performed using the glass fiber filter binding assay procedure with either rabbit reticulocyte lysate or FTase or GGTase I fractions isolated from bovine brains using a combination of hydrophobic and DEAE column chromatography procedures. Protein substrates are purchased from Panvera Corporation (H-ras for FTase, H-ras-CVLL for GGTase I). Tritium labeled prenyl lipid substrates (FPP or GGPP) are obtained from Amersham Life Science.

FTase

^{3}H-Farnesyldiphosphate (final concentration 0.6 μM), H-Ras (final concentration 5.0 μM) and the test compound (various final concentrations from a stock solution in 50% DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM HEPES (pH 7.5), 30 mM $MgCl_2$, 20 mM KCl, 10 μM $ZnCl_2$, 5 mM DTT, 0.01% Triton X-100) to give

a final volume of 50 µL. The mixture was brought to 37 °C, enzyme was added, and the reaction is incubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial and 5 mL of scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC_{50} value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

GGTase I

^{3}H-geranylgeranyldiphosphate (final concentration 0.5 µM), H-Ras-CVLL (final concentration 5.0 µM) and the test compound (various final concentrations from a stock solution in 1:1 DMSO/water; final concentration DMSO < 2%) were mixed in buffer (50 mM Tris-HCl (pH 7.2), 30 mM $MgCl_2$, 20 mM KCl, 10 µM $ZnCl_2$, 5 mM DTT, 0.01% Triton X-100) to give a final volume of 50 µL. The mixture was brought to 37 °C, treated with enzyme, andincubated for 30 minutes. 1 mL of 1 M HCl/ethanol was added to stop the reaction, and the mixture was allowed to stand for 15 minutes at room temperature then diluted with 2 mL of ethanol. The reaction mixture was filtered through a 2.5 cm glass microfiber filter from Whatman and washed with four 2 mL portions of ethanol. The glass filter was transferred to a scintillation vial, and 5 mL scintillation fluid was added. The radioisotope retained on the glass fiber filter was counted to reflect the activity of the enzymes. The IC_{50} value was calculated by measuring the activity of the enzyme over a suitable range of inhibitor concentrations.

Additionally, the ability of the compounds of the invention to inhibit prenylation in whole cells, inhibit anchorage-independent tumor cell growth and inhibit human tumor xenograft in mice could be demonstrated according to the methods described in PCT Patent Application No. WO95/25086, published September 21, 1995, which is hereby incorporated herein by reference.

Pharmaceutical Compositions

The compounds of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. These salts include, but are not limited to, the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate,

glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides (such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides), dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I)-(XII) or separately by reacting the carboxylic acid function with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Such pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

The compounds of the invention are useful (in humans and other mammals) for inhibiting protein isoprenyltransferases (i.e, protein farnesyltransferase and/or protein geranylgeranyltransferase) and the isoprenylation (i.e., farnesylation and/or geranylgeranylation) of Ras. These inhibitors of protein isoprenyltransferases are also useful for inhibiting or treating cancer in humans and other mammals. Examples of cancers which may be treated with the compounds of the invention include, but are not limited to, carcinomas such as lung, colorectal, bladder, breast, kidney, ovarian, liver, exocrine pancreatic, cervical, esophageal, stomach and small intestinal; sarcomas such as oesteroma, osteosarcoma, lepoma, liposarcoma, hemanioma and hemangiosarcoma; melanomas such as amelanotic and melanotic; mixed types of cancers such as carcinosarcoma, lymphoid tissue type, follicular reticulum, cell sarcoma and Hodgkins disease and leukemias, such as

myeloid, acute lymphoblastic, chronic lymphocytic, acute myloblastic and chronic mylocytic.

The ability of the compounds of the invention to inhibit or treat cancer can be demonstrated according to the methods of Mazerska Z., Woynarowska B., Stefanska B., Borowski S., Drugs Exptl. Clin. Res. 13(6), 345-351 (1987) Bissery, M.C., Guenard F., Guerritte-Voegelein F., Lavelle F., Cancer Res. 51, 4845-4852 (1991) and Rygaard J., and Povlsen C., Acta Pathol. Microbiol. Scand. 77, 758 (1969), which are hereby incorporated herein by reference.

These inhibitors of protein isoprenyltransferases are also useful for treating or preventing restenosis in humans and other mammals. The ability of the compounds of the invention to treat or prevent restenosis can be demonstrated according to the methods described by Kranzhofer, R. et al. Circ. Res. 73: 264-268 (1993), Mitsuka, M. et al. Circ. Res. 73: 269-275 (1993) and Santoian, E.C. et al. Circulation 88: 11-14 (1993), which are hereby incorporated herein by reference.

For use as a chemotherapeutic agent, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.01 to 500 mg/kg body weight daily, preferably in amounts from 0.1 to 20 mg/kg body weight daily and more preferably in amounts from 0.5 to 10 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

For treatment or prevention of restenosis, the total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention may be administered orally, parenterally, sublingually, by inhalation spray, rectally or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes

subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques.

Injectable preparations, for example sterile injectable aqueous or oleagenous suspensions, may be formulated according to the known art using suitable dispersing or wetting and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent (as in a solution in 1,3-propanediol, for example). Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Additionally, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. These dosage forms may also comprise additional substances other than inert diluents such as lubricating agents like magnesium stearate. With capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills mayalso be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents, emulsifying and suspending agents and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals dispersed in an aqueous medium. Any non-toxic, physiologically aceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 *et seq.*, which is hereby incorporated herein by reference.

While the compounds of the invention can be administered as the sole active pharmaceutical agent for the treatment of cancer, they can also be used in combination with one or more other chemotherapeutic agents.

Representative examples of chemotherapeutic agents are described in Holleb, et al., Clinical Oncology, American Cancer Society, United States (1991) p 56 *et seq.*, which is hereby incorporated herein by reference These agents include alkylating agents such as the nitrogen mustards (mechloethamine, melphalan, chlorambucil, cyclophosphamide and ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), alkyl sulfonates (busulfan), triazines (dacarbazine) and ethyenimines (thiotepa, hexamethylmelamine); folic acid analogues (methotrexate); pyrimidine analogues (5-fluorouracil, cytosine arabinoside); purine analogues (6-mercaptopurine, 6-thioguanine); antitumor antibiotics (actinomycin D, the anthracyclines (doxorubicin), bleomycin, mitomycin C, methramycin); plant alkaloids such as vinca alkaloids (vincristine and vinblastine) and etoposide (VP-16); hormones and hormone antagonists (tamoxifen and corticosteroids); and miscellaneous agents (cisplatin, taxol and brequinar).

The above compounds to be employed in combination with the isoprenyl protein transferase inhibitor of the invention will be used in therapeutic amounts as indicated in the Physicians' Desk Reference (PDR) 47th Edition (1993), which is incorporated herein by reference or by such therapeutically useful amounts as would be known to one of ordinary skill in the art.

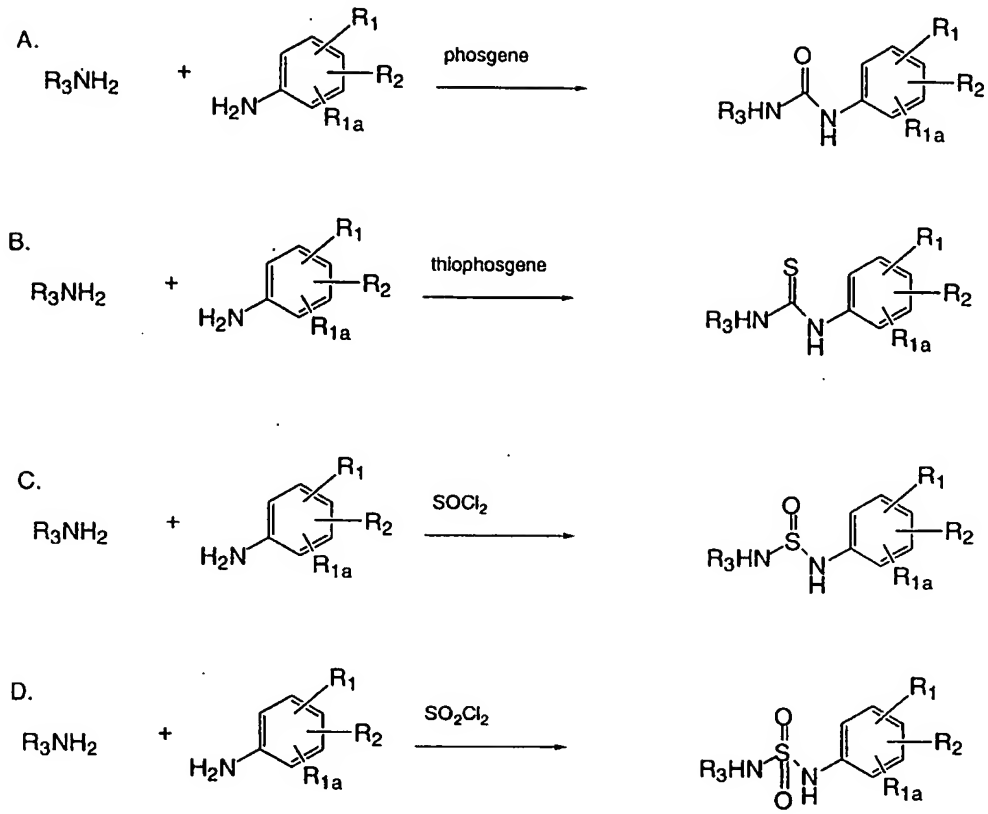
The compounds of the invention and the other chemotherapeutic agent can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient.

When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

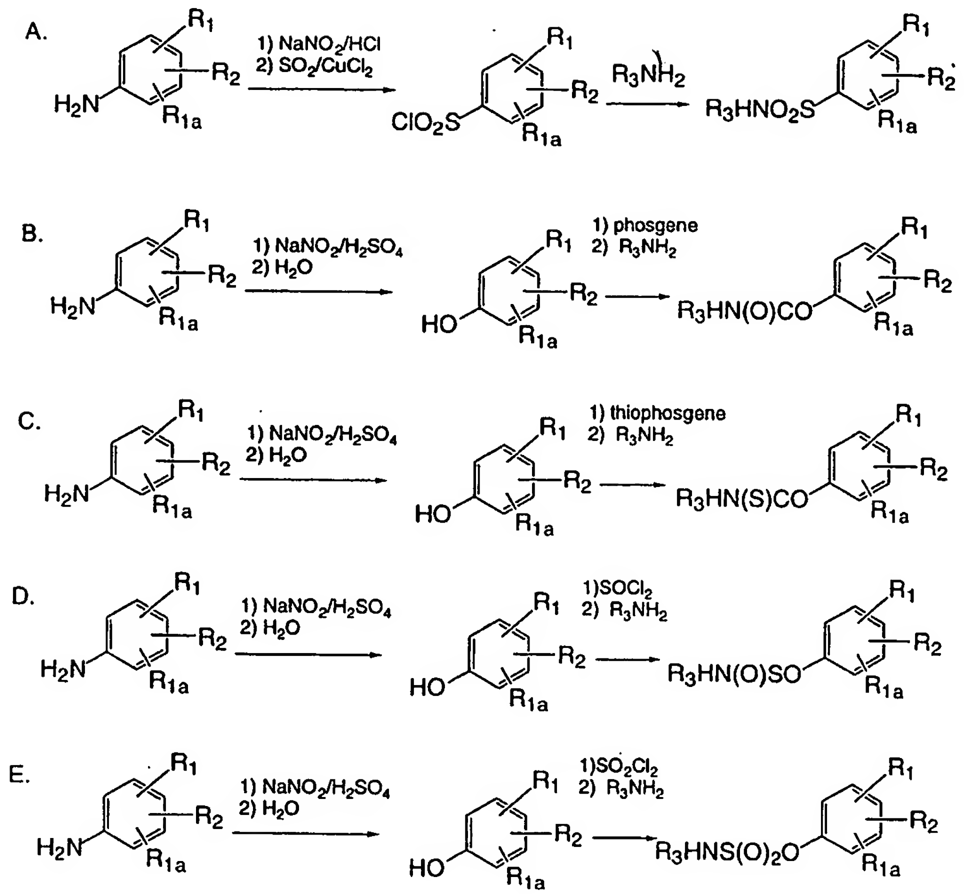
Preparation of the Compounds of the Invention

In general, the compounds of the invention can be prepared by the processes illustrated in the following Schemes 1-16. In these general schemes compounds of the formula I are used to exemplify the methods, but the methods are intended to be applicable to all of the compounds of the invention.

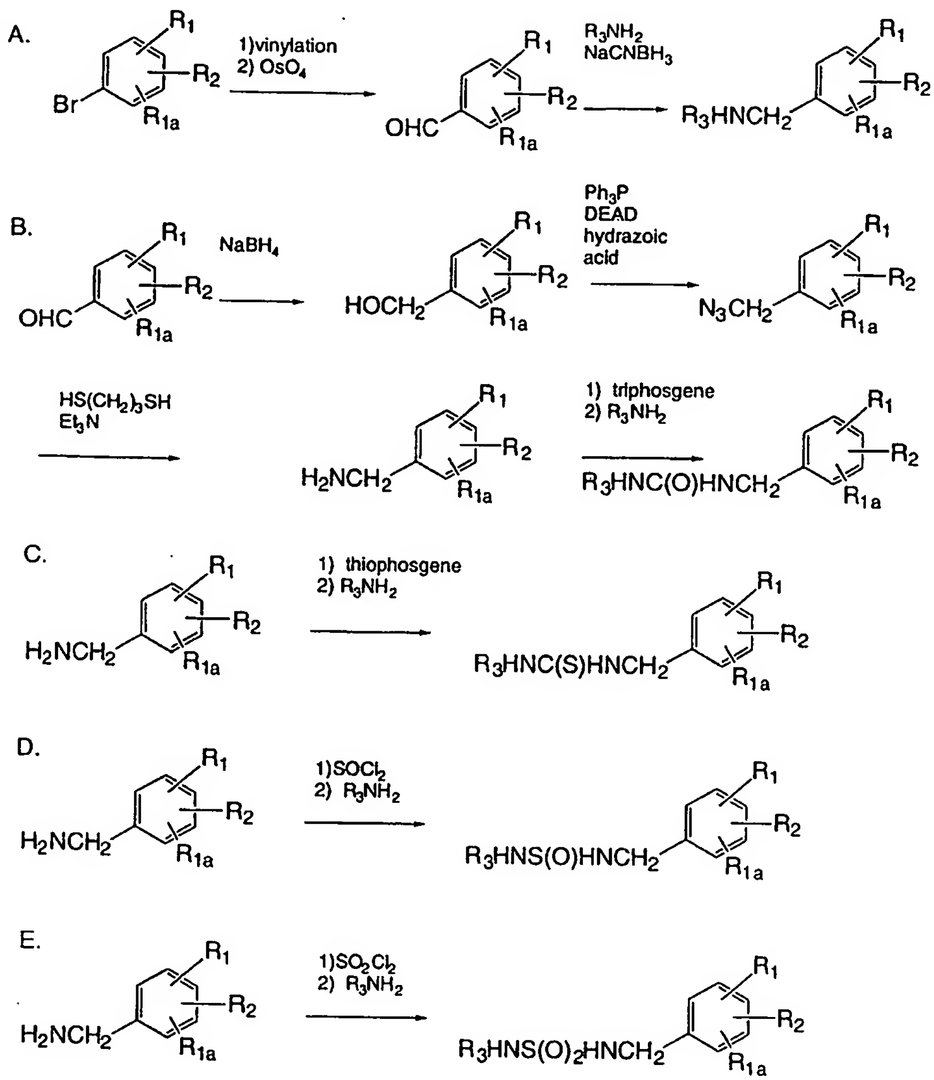
SCHEME 1


A.
R_3NH_2
+
H_2N
R_1
R_2
R_{1a}
phosgene
R_3HN
O
N
H
B.
thiophosgene
S
C.
$SOCl_2$
D.
SO_2Cl_2

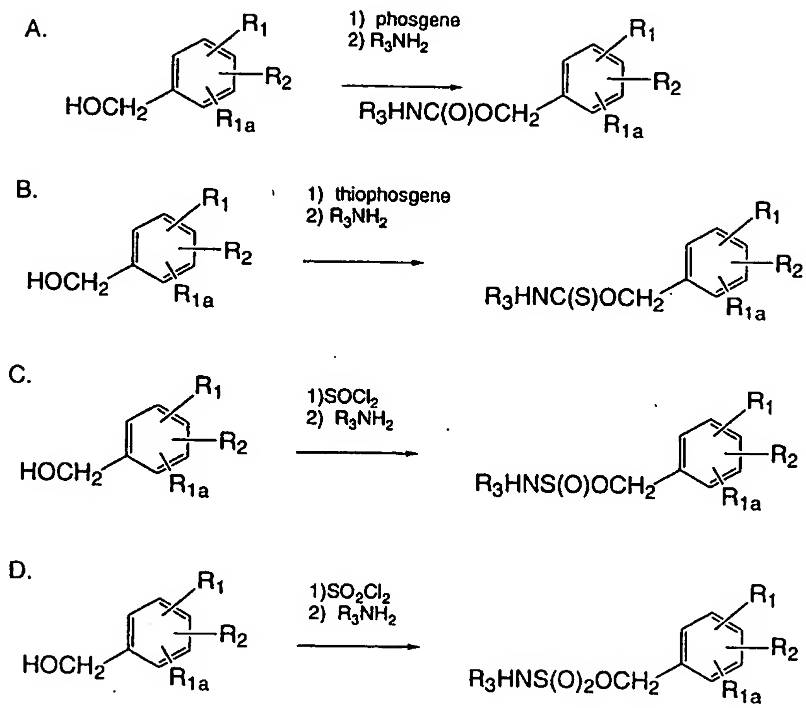
SCHEME 2


A.
1) NaNO2/HCl
2) SO2/CuCl2
R3NH2
B.
1) NaNO2/H2SO4
2) H2O
1) phosgene
2) R3NH2
C.
1) NaNO2/H2SO4
2) H2O
1) thiophosgene
2) R3NH2
D.
1) NaNO2/H2SO4
2) H2O
1)SOCl2
2) R3NH2
E.
1) NaNO2/H2SO4
2) H2O
1)SO2Cl2
2) R3NH2

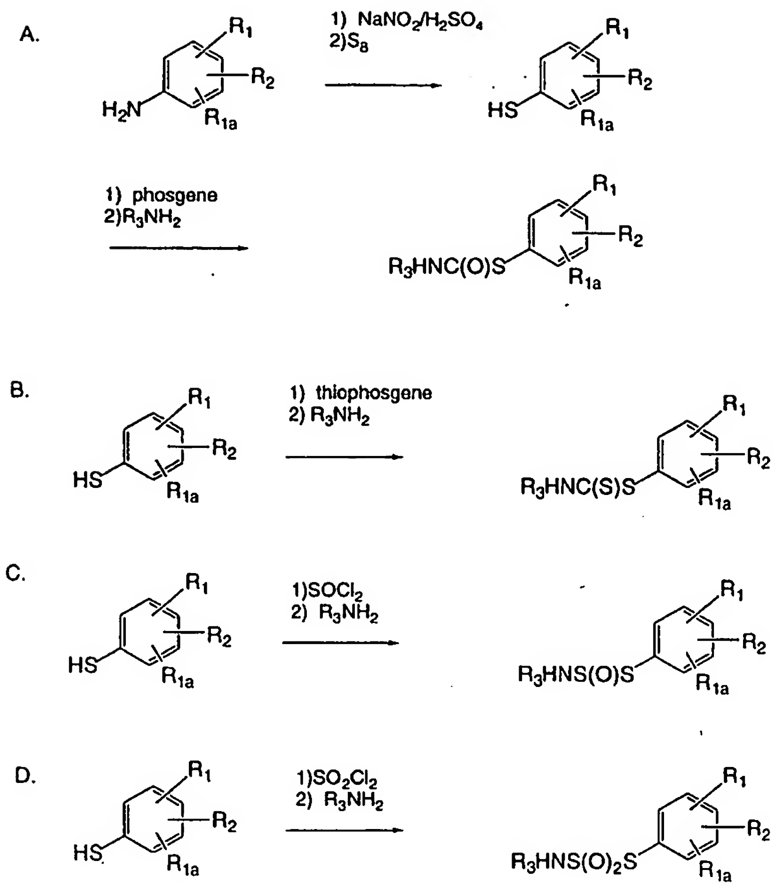
SCHEME 3



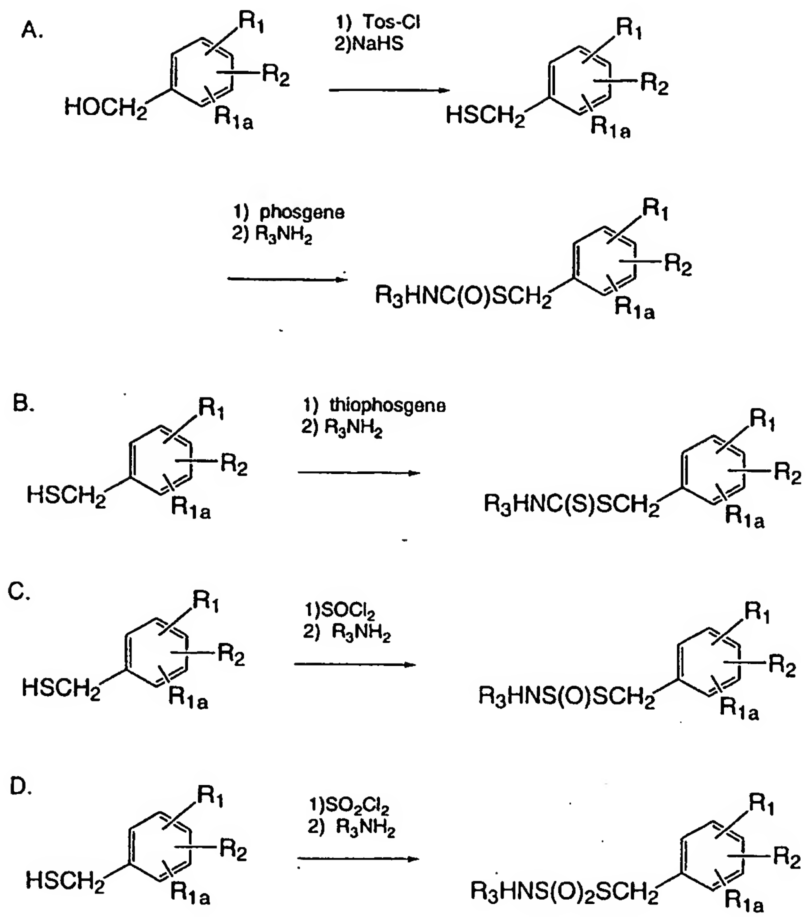
SCHEME 4


A.
R1
R2
HOCH2
R1a
1) phosgene
2) R3NH2
R3HNC(O)OCH2
B.
1) thiophosgene
2) R3NH2
R3HNC(S)OCH2
C.
1)SOCl2
2) R3NH2
R3HNS(O)OCH2
D.
1)SO2Cl2
2) R3NH2
R3HNS(O)2OCH2

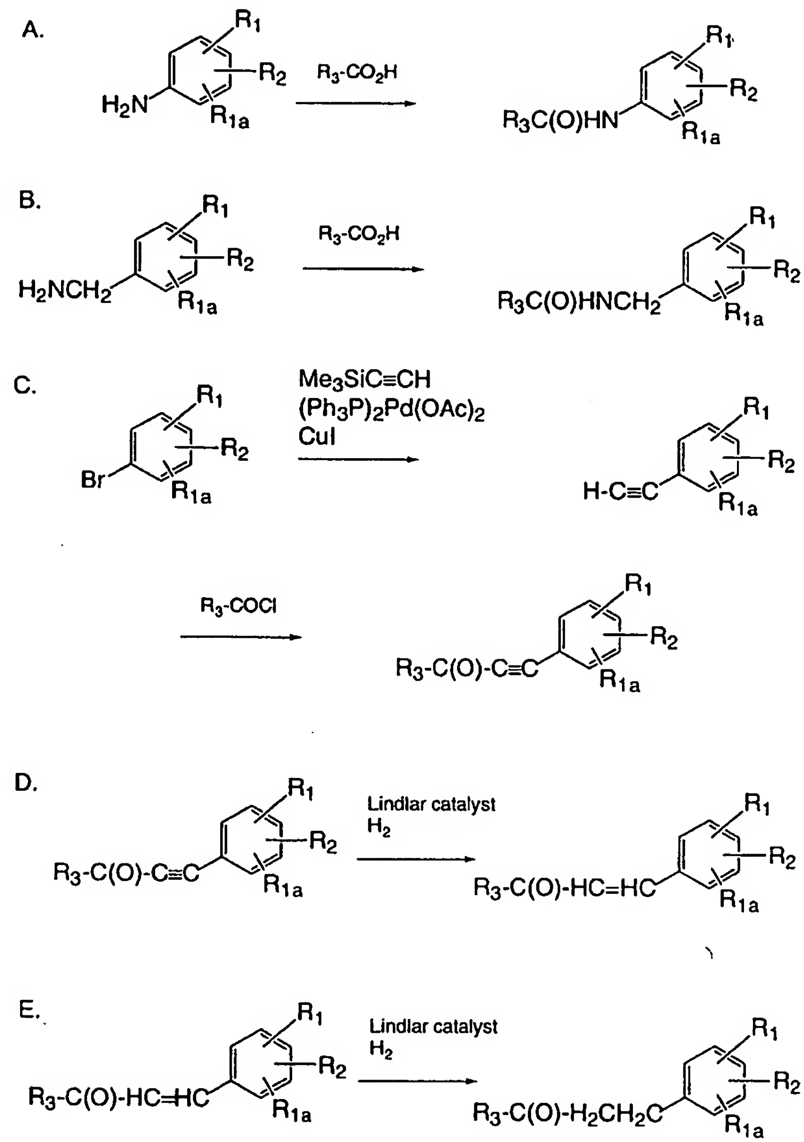
SCHEME 5


A.
1) NaNO2/H2SO4
2)S8
1) phosgene
2)R3NH2
R3HNC(O)S
B.
1) thiophosgene
2) R3NH2
R3HNC(S)S
C.
1)SOCl2
2) R3NH2
R3HNS(O)S
D.
1)SO2Cl2
2) R3NH2
R3HNS(O)2S
H2N
HS
R1
R2
R1a

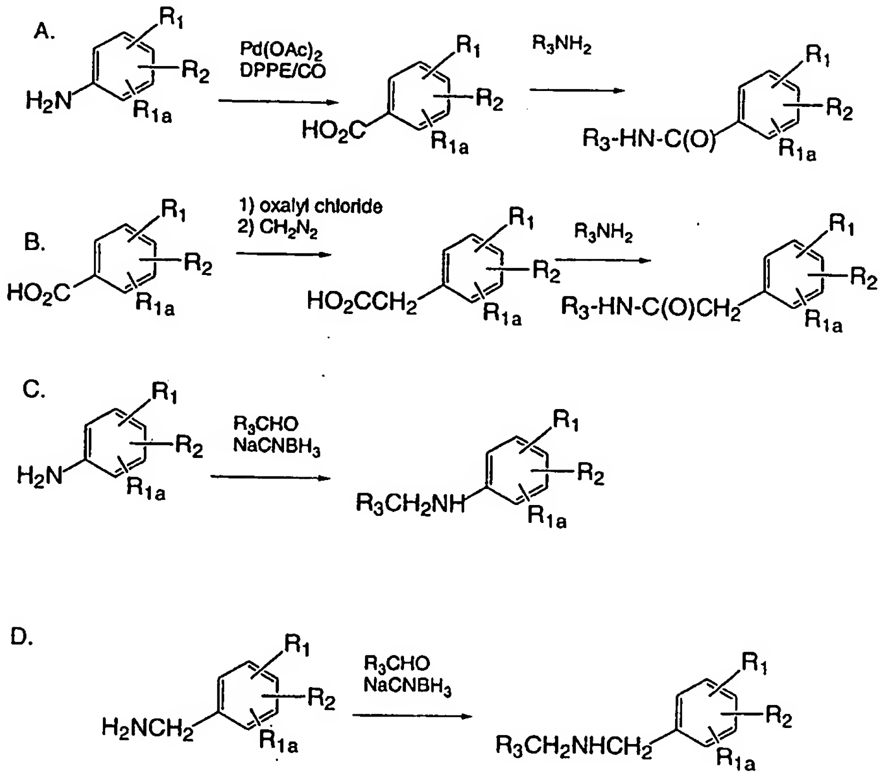
SCHEME 6


A.
1) Tos-Cl
2)NaHS
HOCH2
HSCH2
1) phosgene
2) R3NH2
R3HNC(O)SCH2
B.
1) thiophosgene
2) R3NH2
HSCH2
R3HNC(S)SCH2
C.
1)SOCl2
2) R3NH2
HSCH2
R3HNS(O)SCH2
D.
1)SO2Cl2
2) R3NH2
HSCH2
R3HNS(O)2SCH2
R1
R2
R1a

SCHEME 7

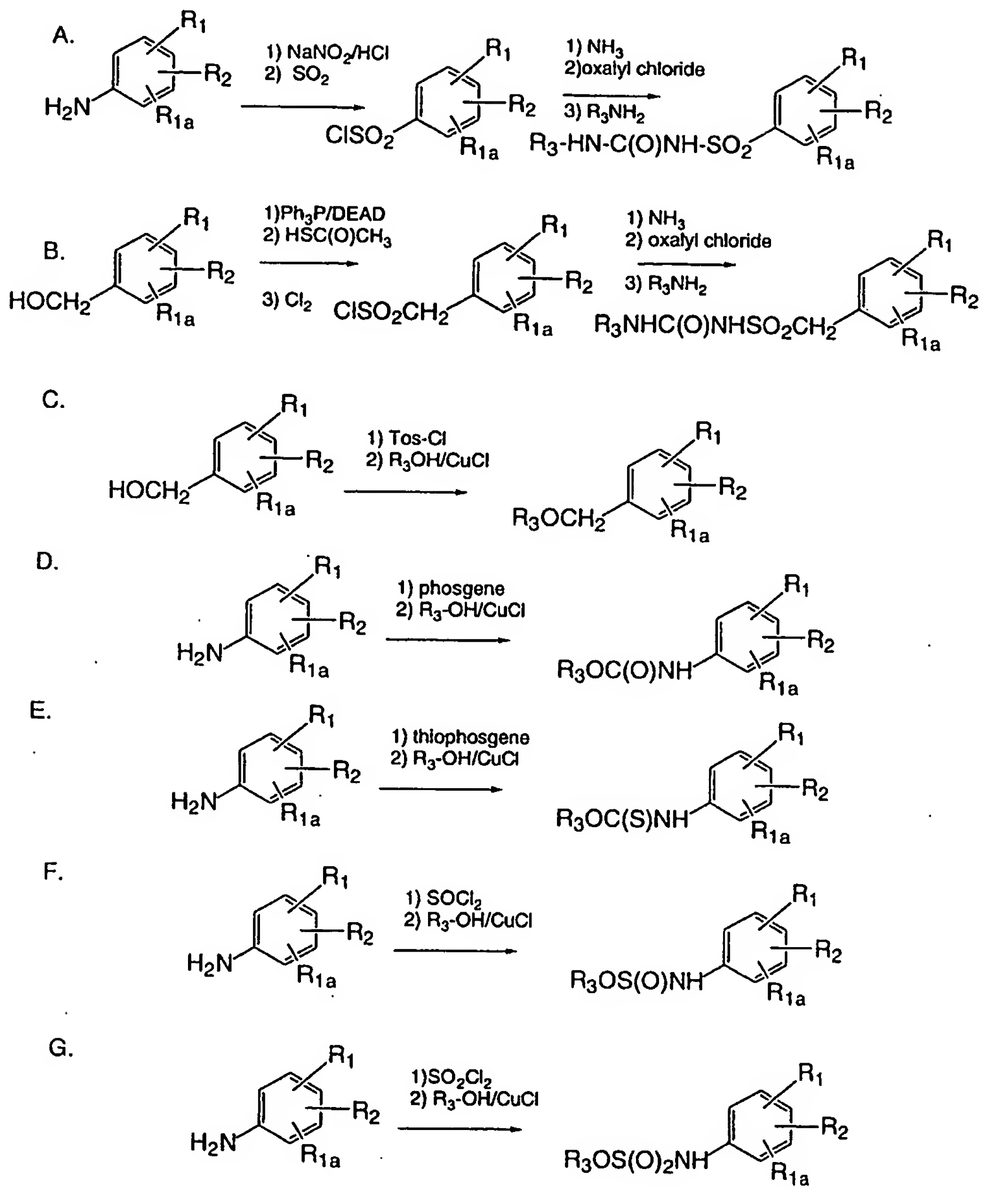

A.
R1
R2
H2N
R1a
R3-CO2H
R1
R2
R3C(O)HN
R1a
B.
R1
R2
H2NCH2
R1a
R3-CO2H
R1
R2
R3C(O)HNCH2
R1a
C.
R1
R2
Br
R1a
Me3SiC≡CH
(Ph3P)2Pd(OAc)2
CuI
R1
R2
H-C≡C
R1a
R3-COCl
R1
R2
R3-C(O)-C≡C
R1a
D.
R1
R2
R3-C(O)-C≡C
R1a
Lindlar catalyst
H2
R1
R2
R3-C(O)-HC=HC
R1a
E.
R1
R2
R3-C(O)-HC=HC
R1a
Lindlar catalyst
H2
R1
R2
R3-C(O)-H2CH2C
R1a

SCHEME 8

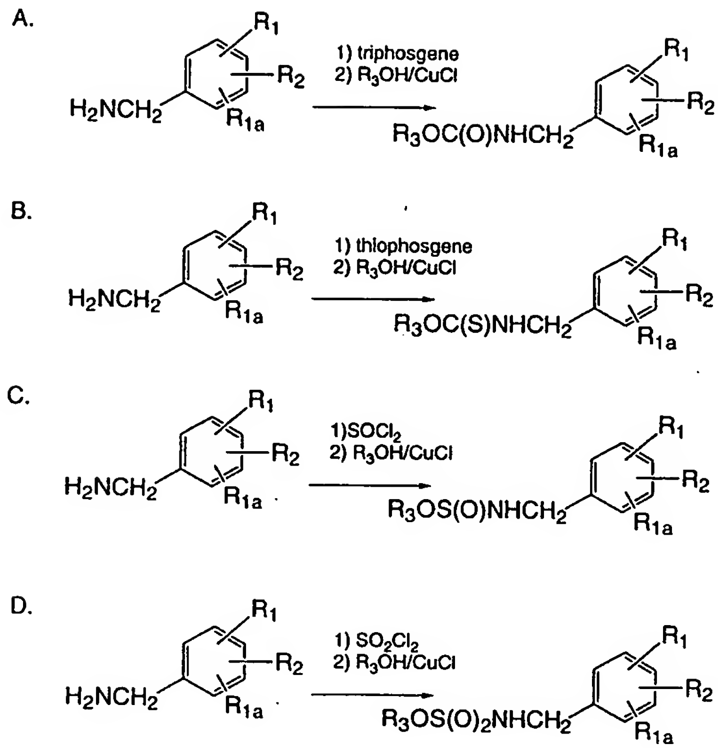


1615

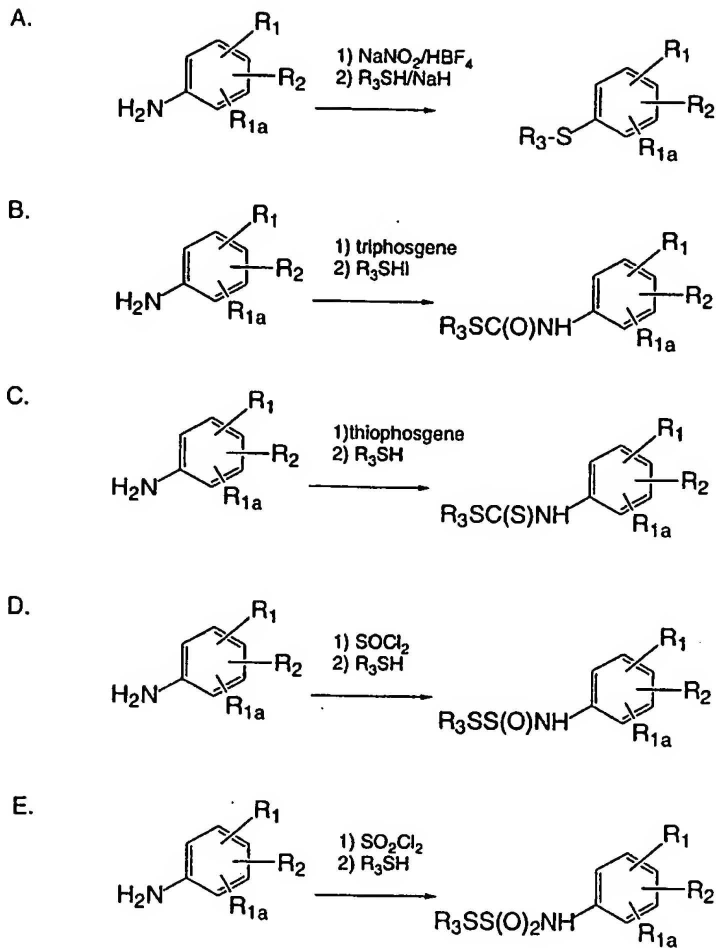
SCHEME 9


A.
1) NaNO2/HCl
2) SO2
1) NH3
2)oxalyl chloride
3) R3NH2
R3-HN-C(O)NH-SO2
B.
1)Ph3P/DEAD
2) HSC(O)CH3
3) Cl2
1) NH3
2) oxalyl chloride
3) R3NH2
R3NHC(O)NHSO2CH2
C.
1) Tos-Cl
2) R3OH/CuCl
R3OCH2
D.
1) phosgene
2) R3-OH/CuCl
R3OC(O)NH
E.
1) thiophosgene
2) R3-OH/CuCl
R3OC(S)NH
F.
1) SOCl2
2) R3-OH/CuCl
R3OS(O)NH
G.
1)SO2Cl2
2) R3-OH/CuCl
R3OS(O)2NH

SCHEME 10

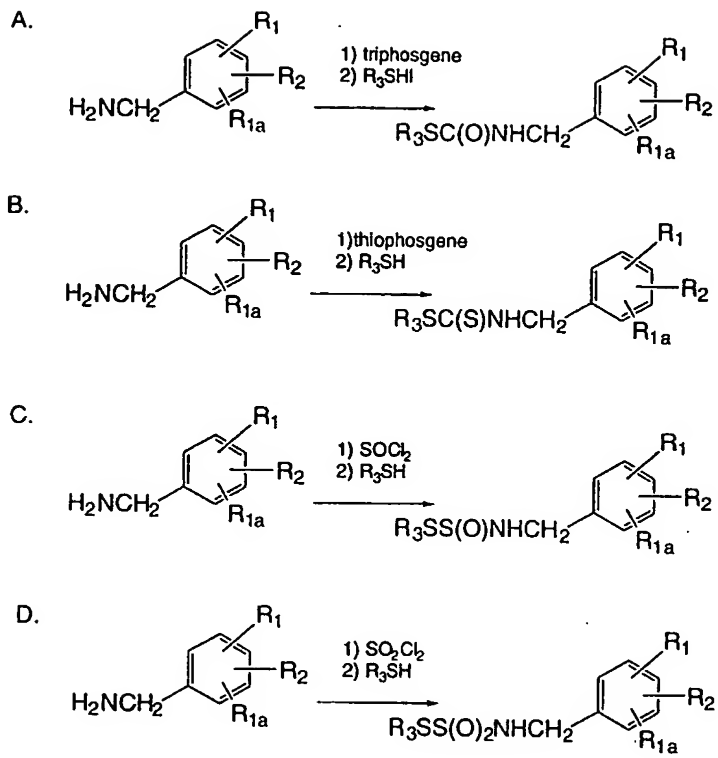

A.
H2NCH2
R1
R2
R1a
1) triphosgene
2) R3OH/CuCl
R3OC(O)NHCH2
B.
1) thiophosgene
2) R3OH/CuCl
R3OC(S)NHCH2
C.
1)SOCl2
2) R3OH/CuCl
R3OS(O)NHCH2
D.
1) SO2Cl2
2) R3OH/CuCl
R3OS(O)2NHCH2

SCHEME 11

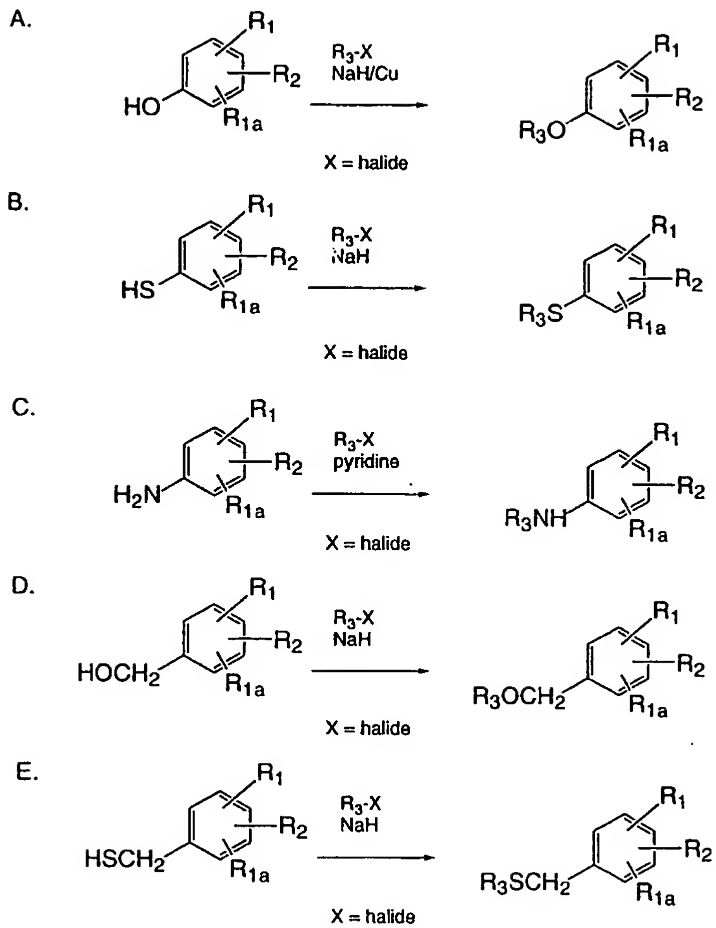


1625

SCHEME 12

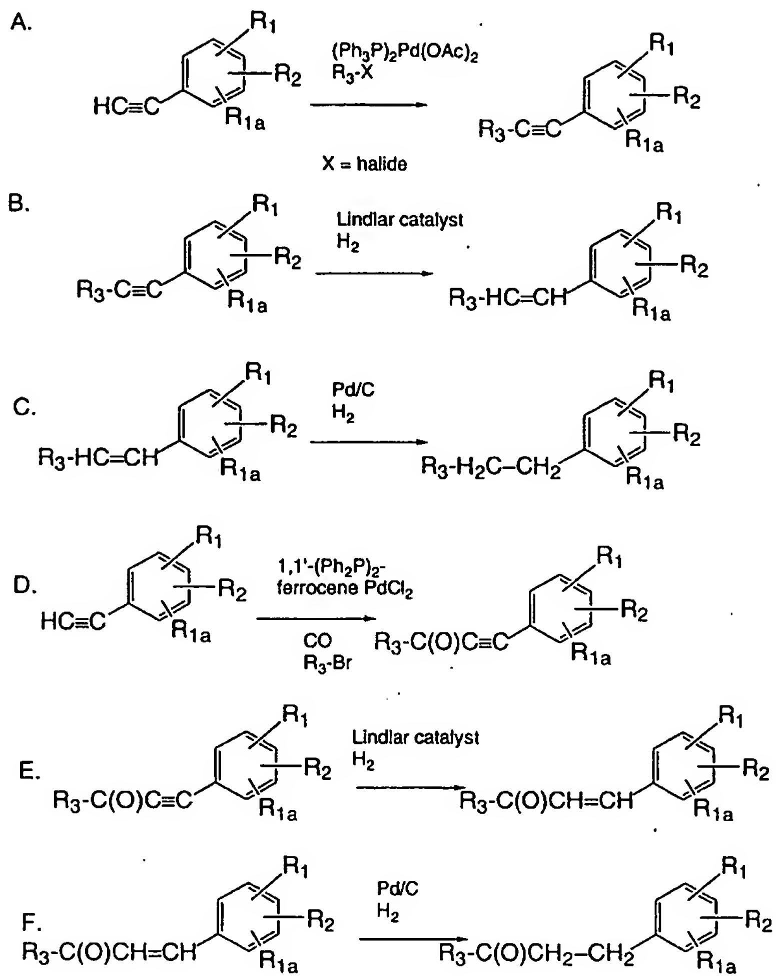

A.
R1
R2
H2NCH2
R1a
1) triphosgene
2) R3SHI
R3SC(O)NHCH2
B.
1)thiophosgene
2) R3SH
R3SC(S)NHCH2
C.
1) SOCl2
2) R3SH
R3SS(O)NHCH2
D.
1) SO2Cl2
2) R3SH
R3SS(O)2NHCH2

SCHEME 13

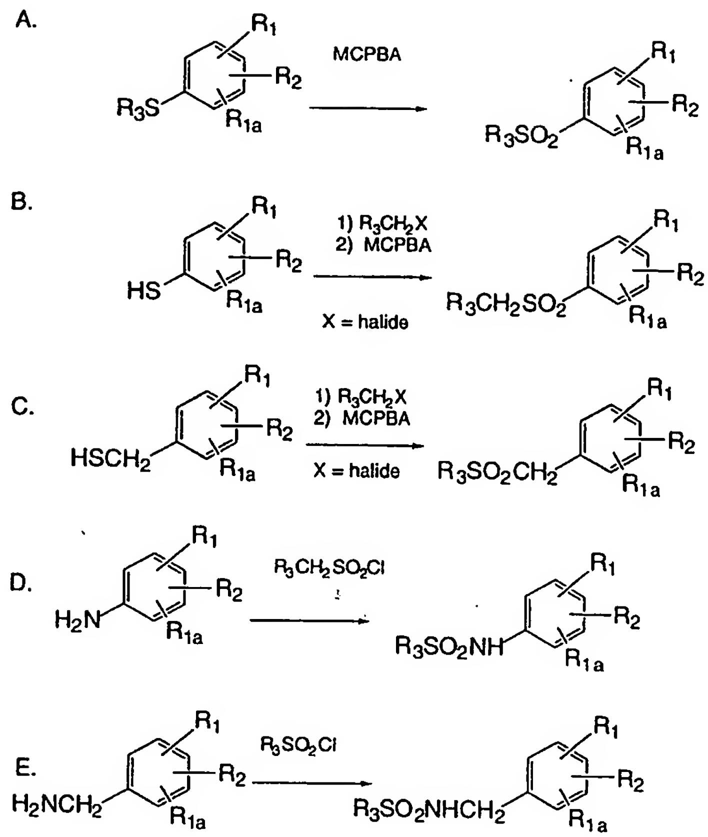


1630

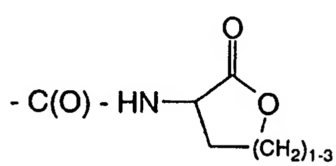
SCHEME 14


A.
(Ph3P)2Pd(OAc)2
R3-X
X = halide
HC≡C
R3-C≡C
B.
Lindlar catalyst
H2
R3-HC=CH
C.
Pd/C
H2
R3-H2C–CH2
D.
1,1'-(Ph2P)2-
ferrocene PdCl2
CO
R3-Br
R3-C(O)C≡C
E.
R3-C(O)CH=CH
F.
R3-C(O)CH2–CH2
R1
R2
R1a

SCHEME 15

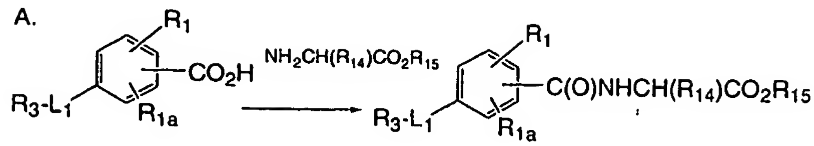


Scheme 16 illustrates an alternative method for preparing compounds wherein R_2 is -C(O)NH-CH(R_{14})-C(O)OR_{15} or



as defined above.

SCHEME 16


A.
R_1
CO_2H
R_3-L_1
R_{1a}
$NH_2CH(R_{14})CO_2R_{15}$
$C(O)NHCH(R_{14})CO_2R_{15}$

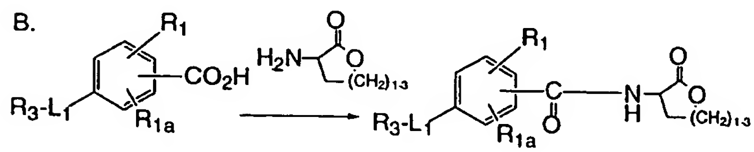
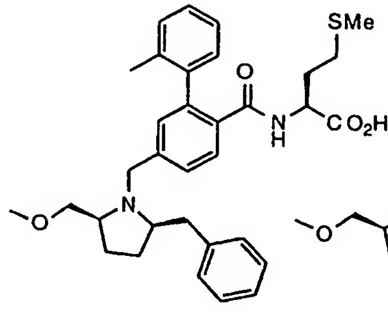
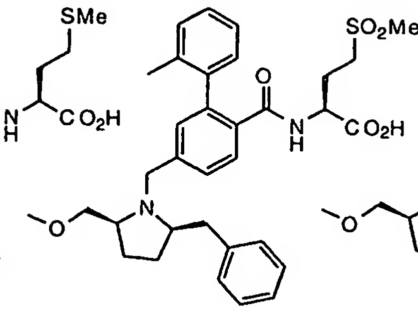
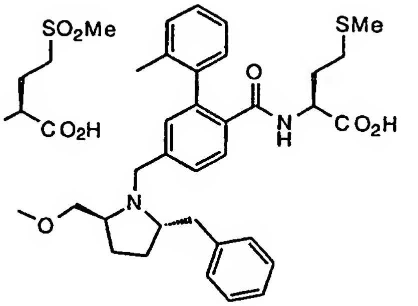
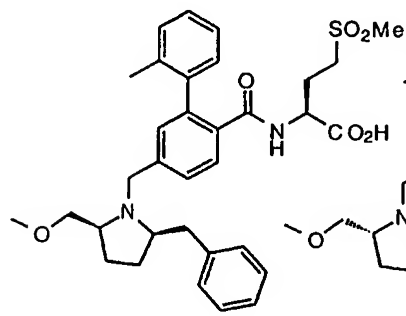
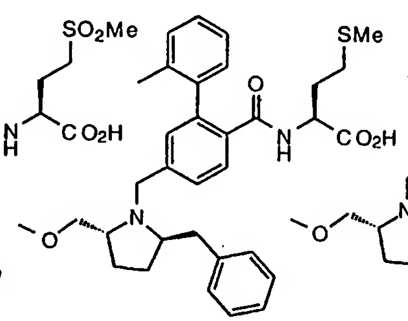
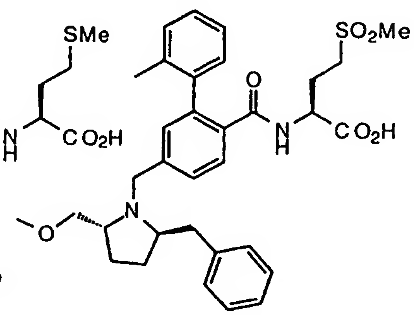

B.
R_1
CO_2H
R_3-L_1
R_{1a}
H_2N
O
$(CH_2)_{1-3}$
C
N
H

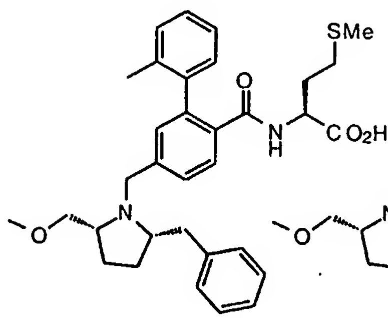
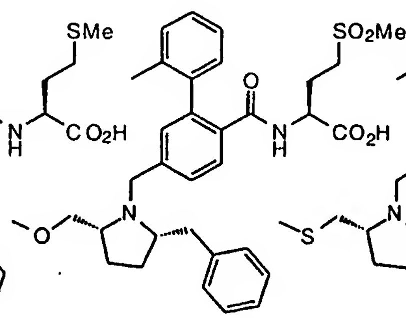
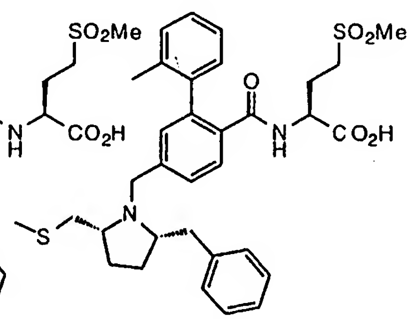
Table 6. Amines of the Type A(B)N-L_1

1 2 3

4 5 6

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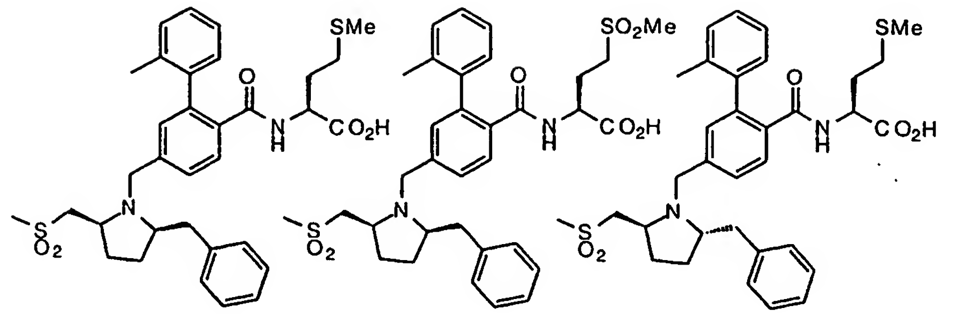

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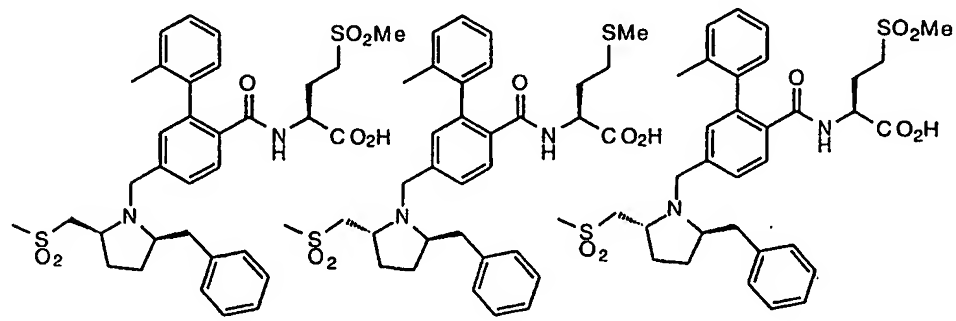

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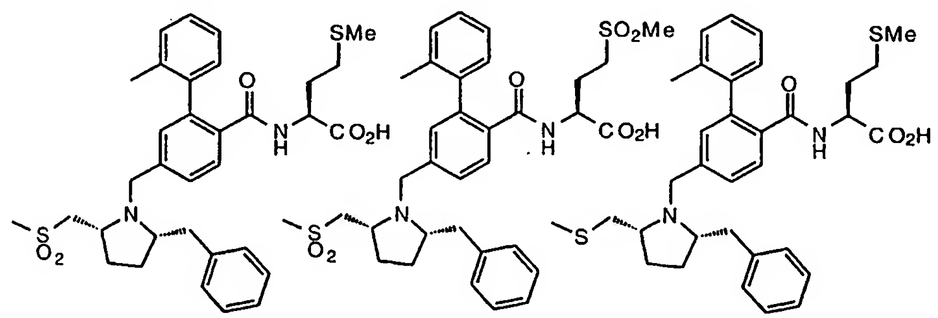

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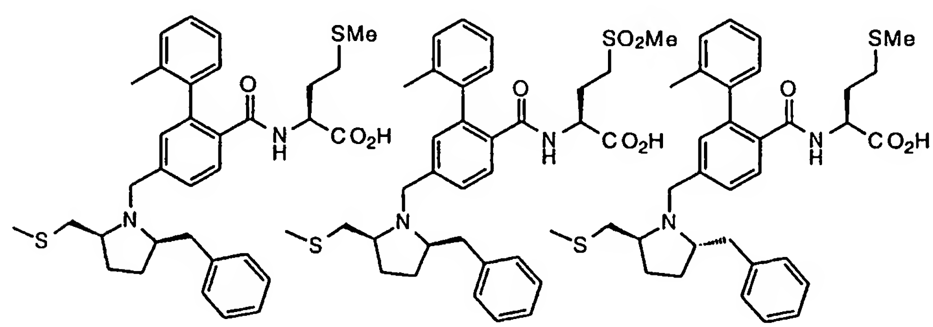

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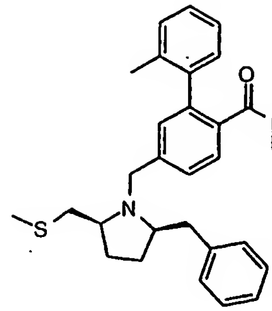
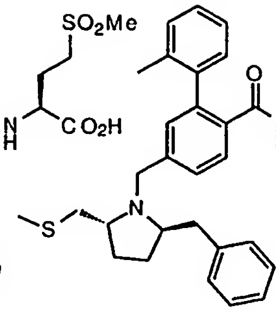
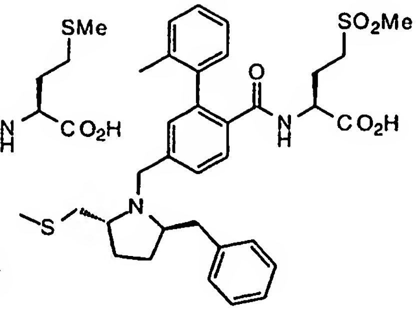

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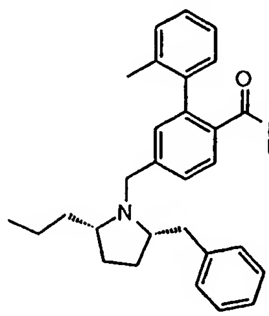
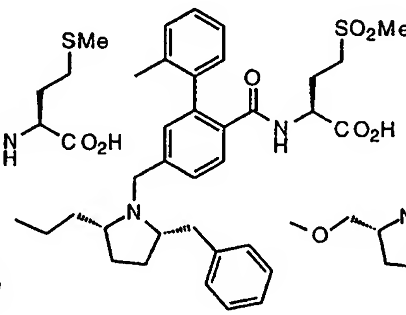
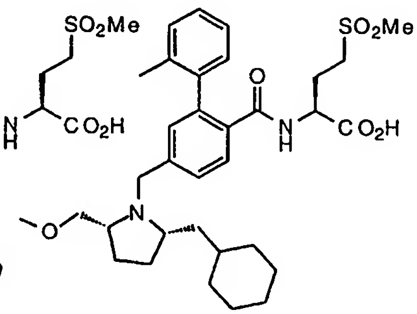
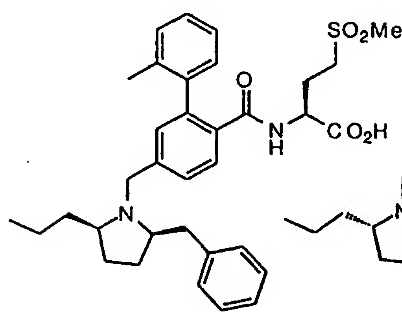
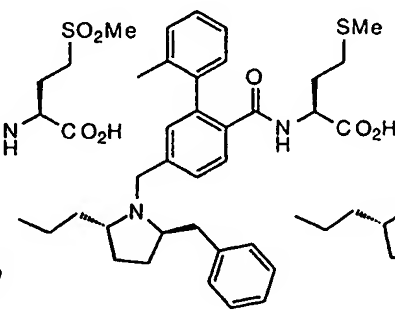
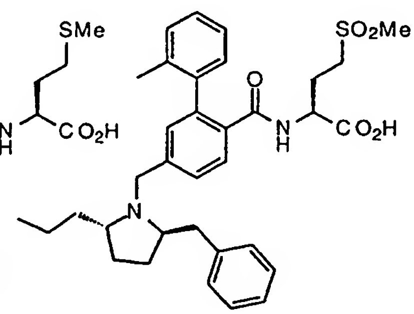




25 26 27

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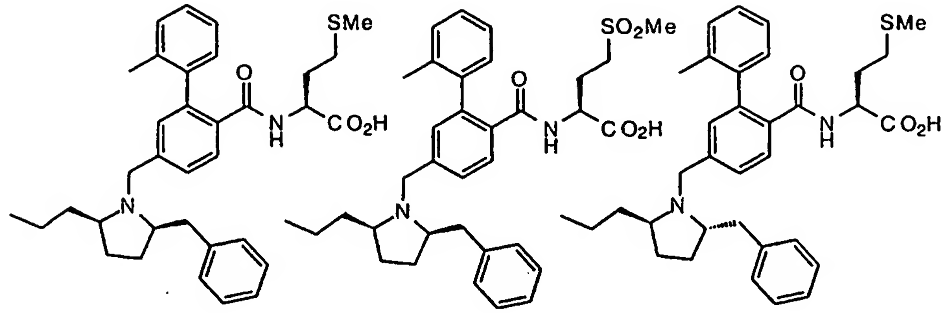

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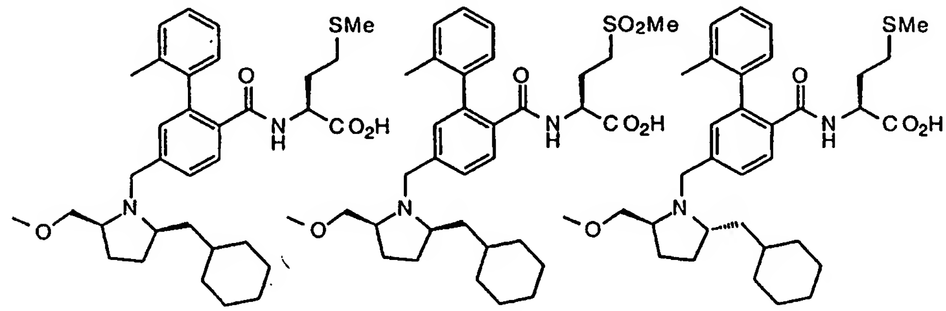

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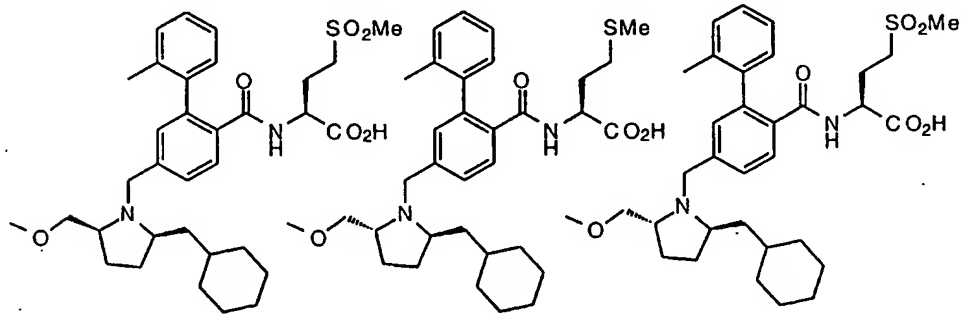

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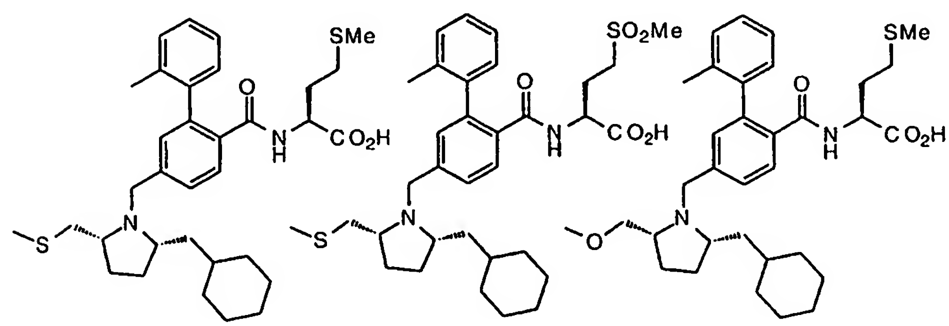

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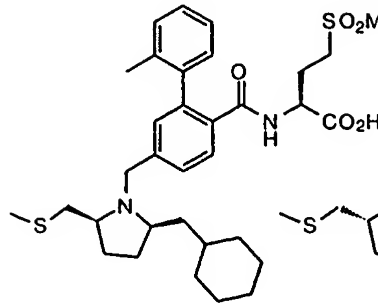
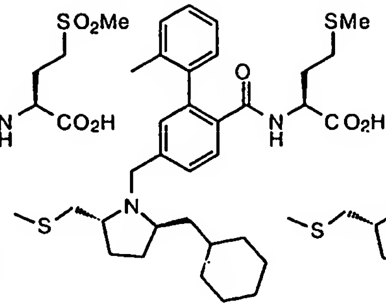
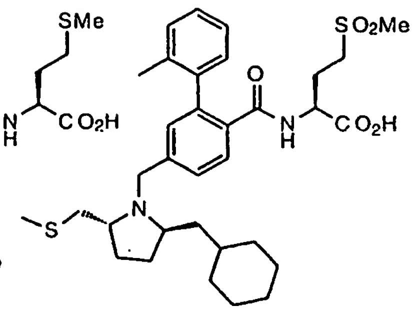

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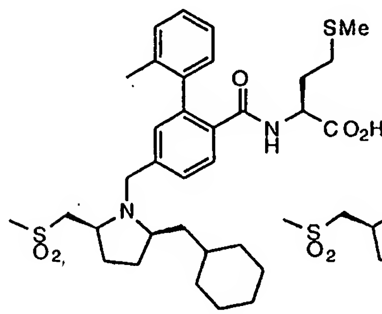
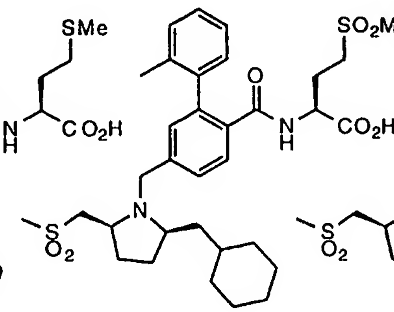
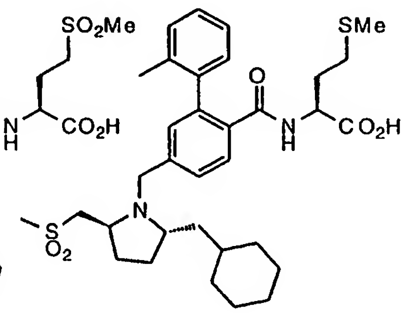

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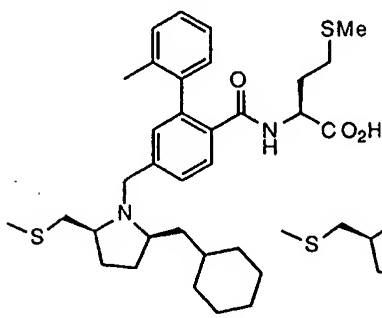
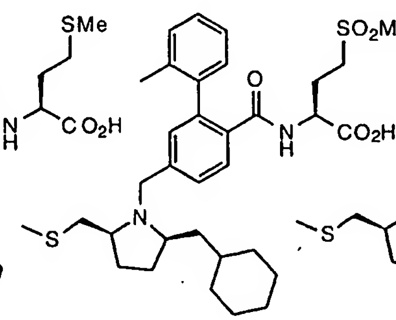
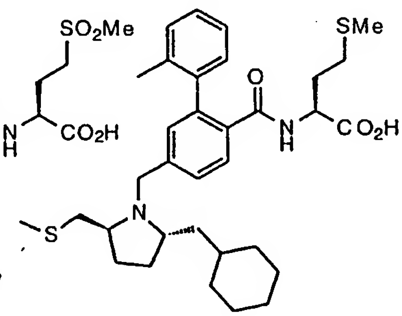

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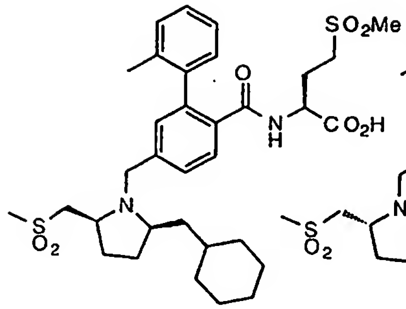 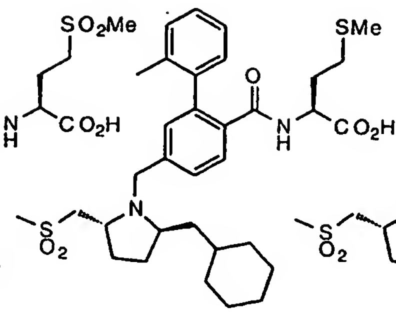 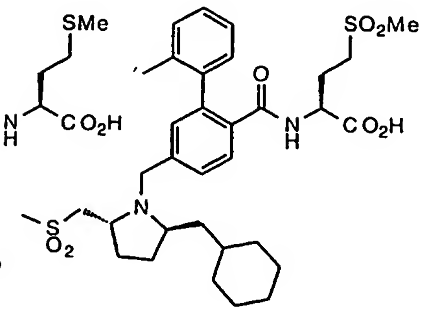

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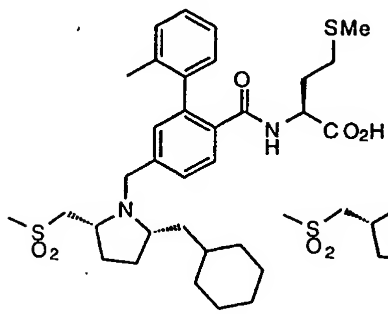 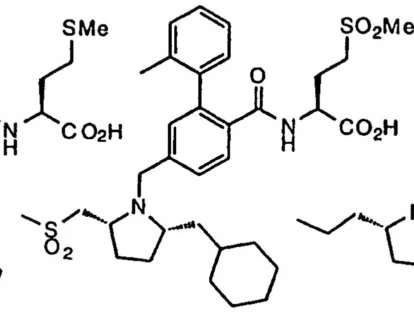 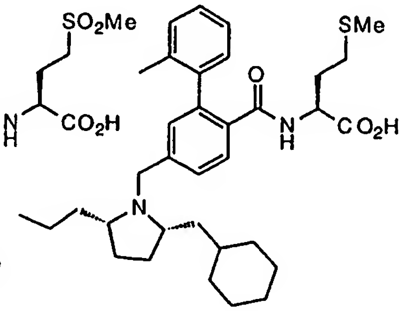

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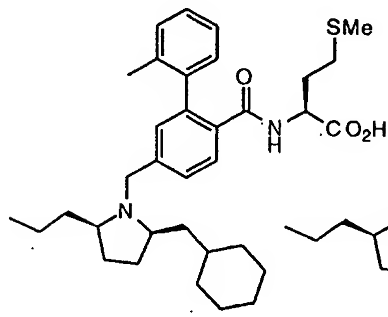 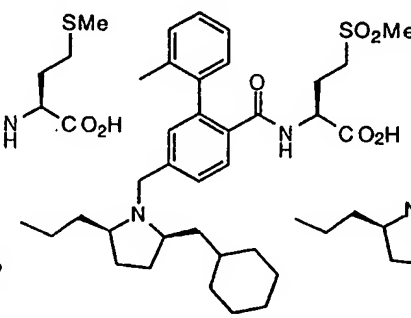 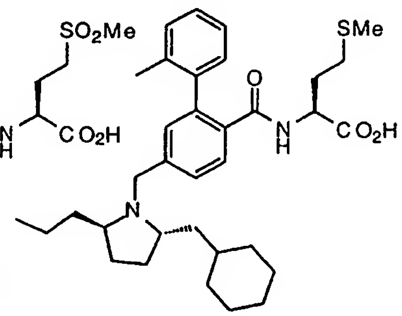

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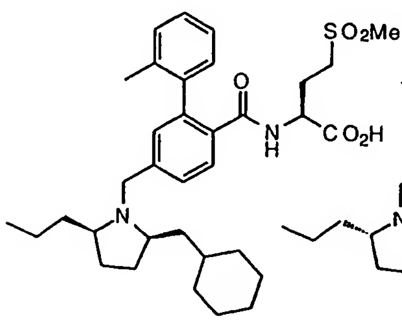 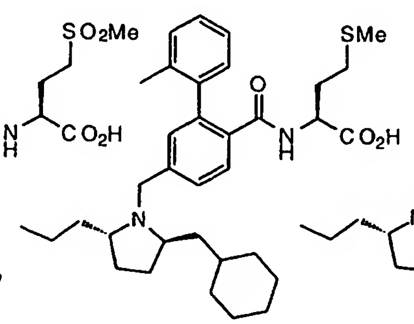 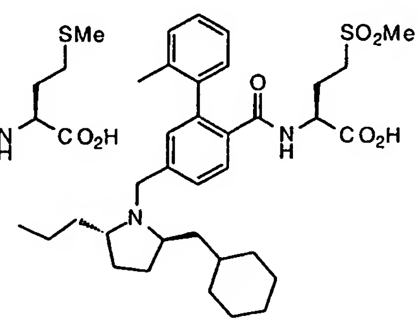

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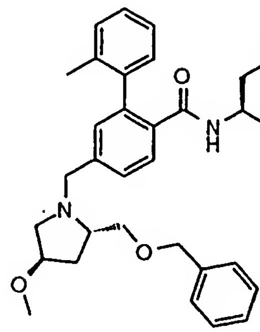
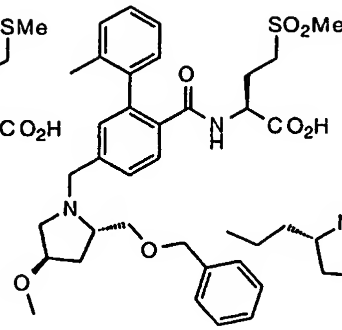
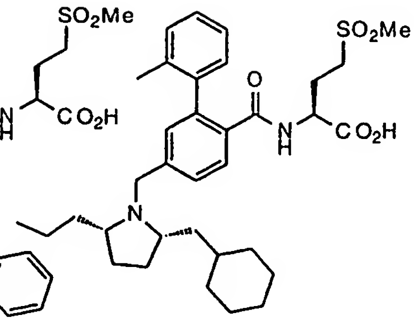

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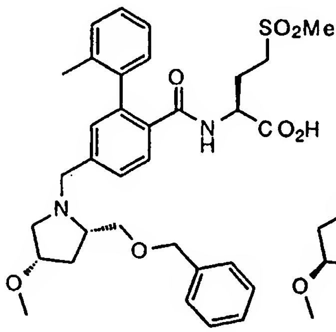
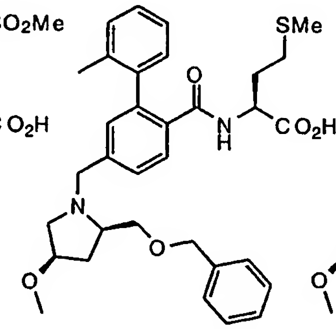
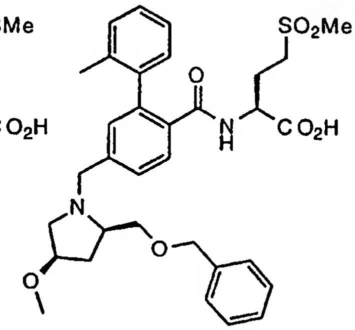

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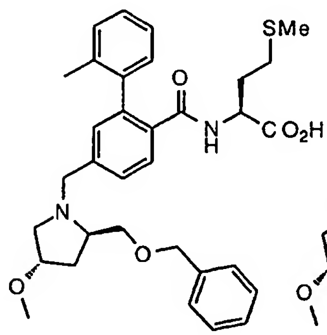
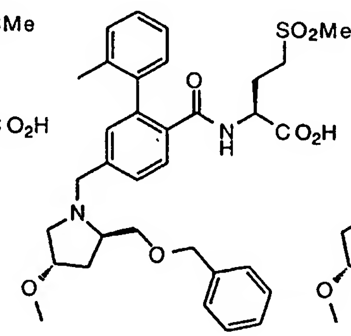
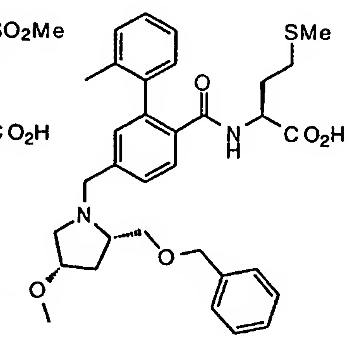

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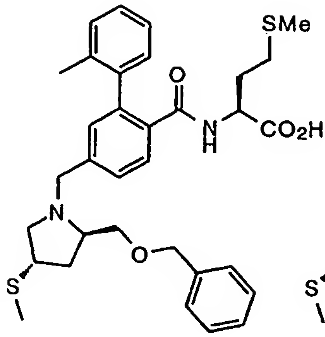 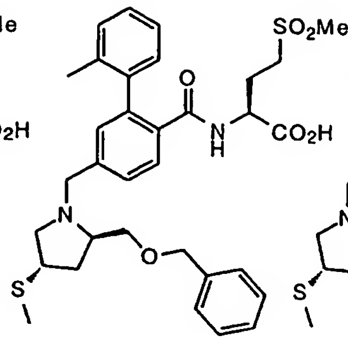 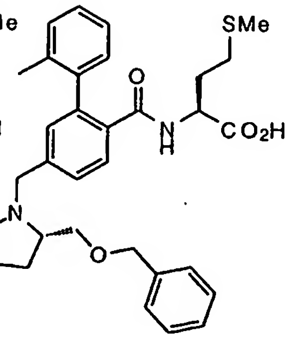

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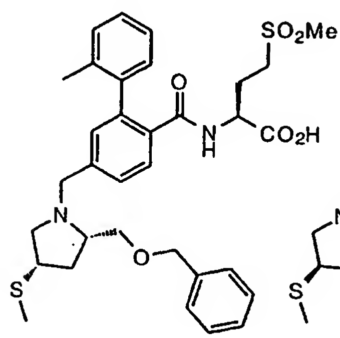 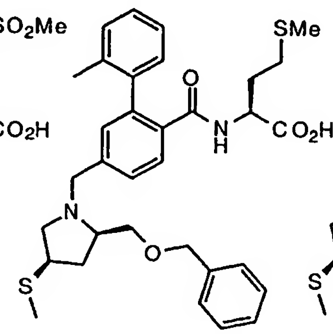 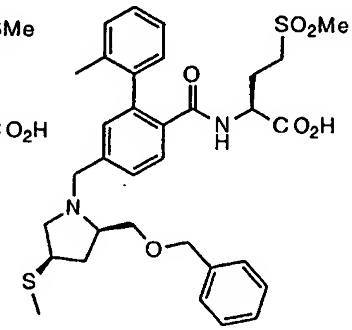

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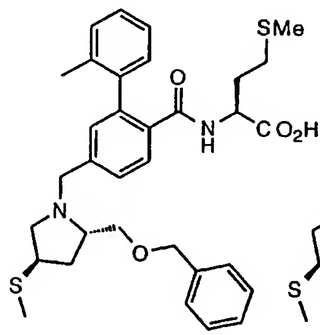 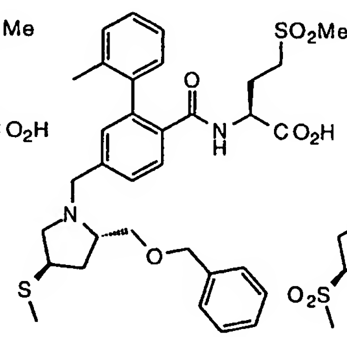 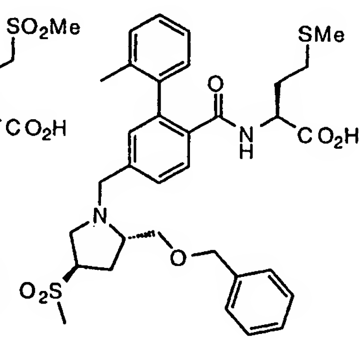

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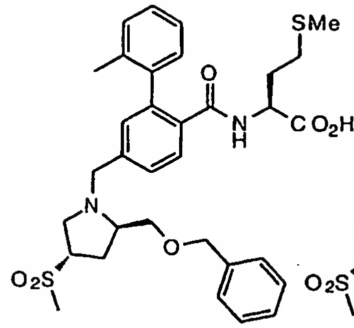
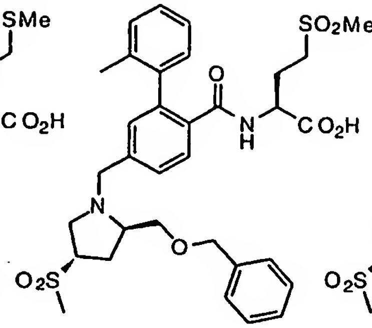
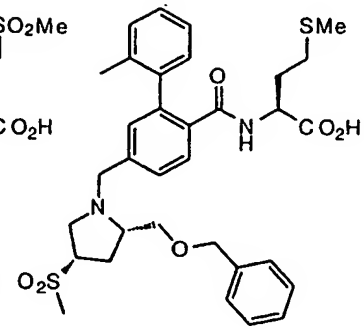

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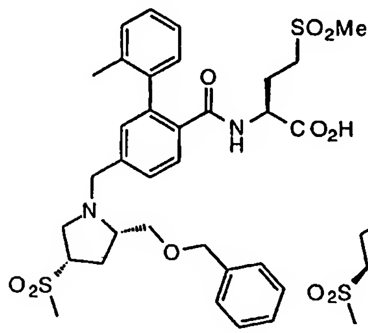
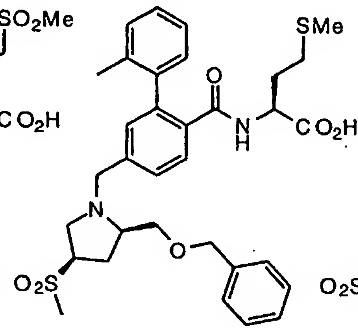
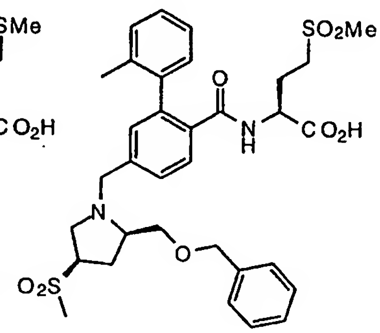

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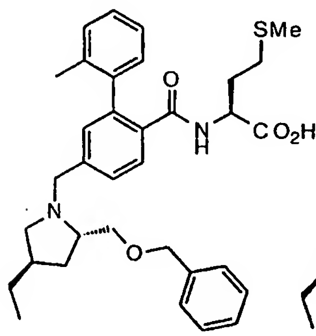
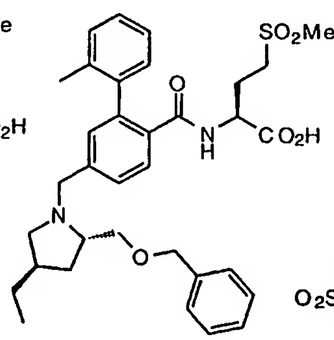
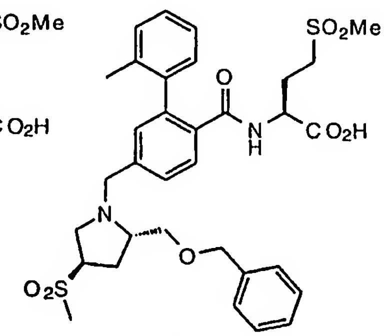

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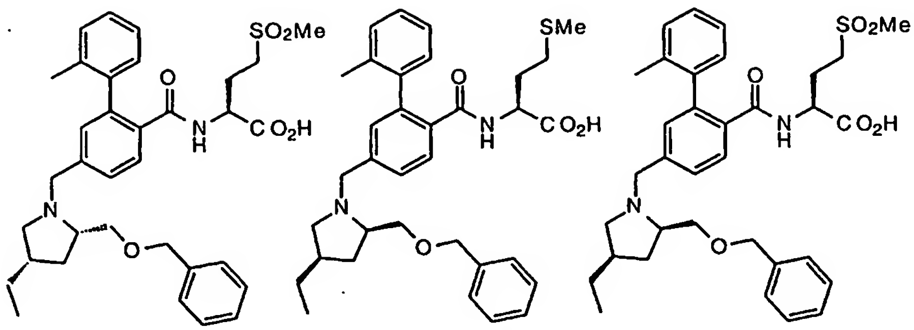

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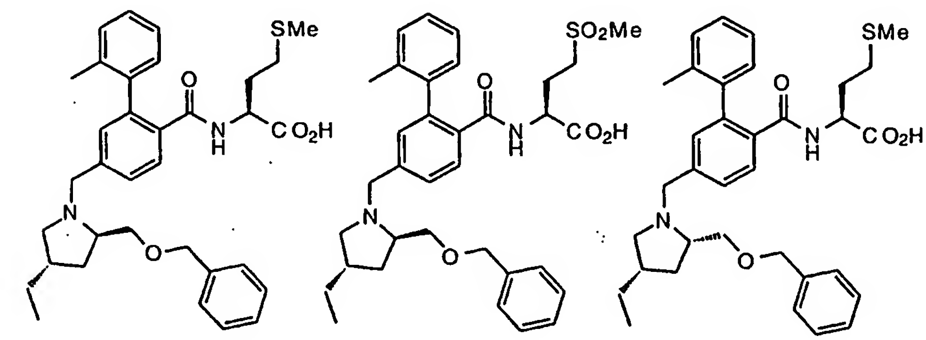

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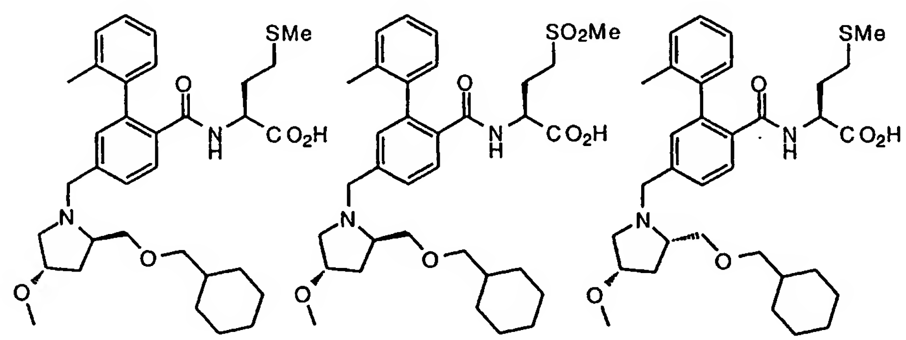

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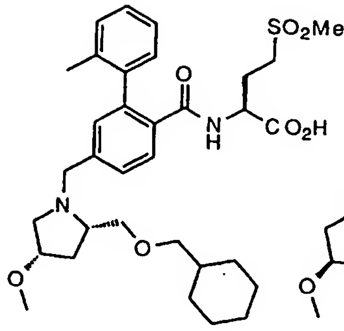
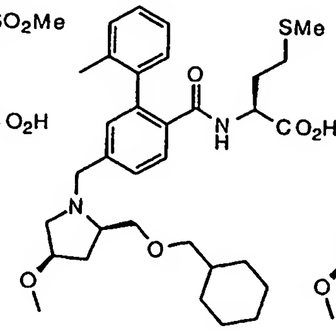
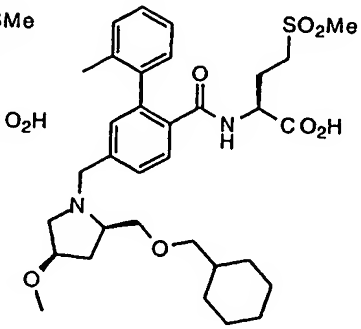

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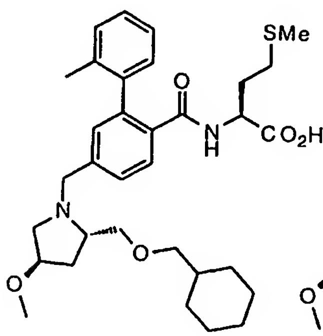
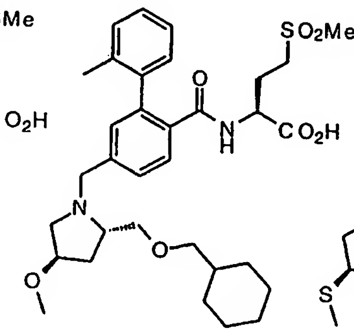
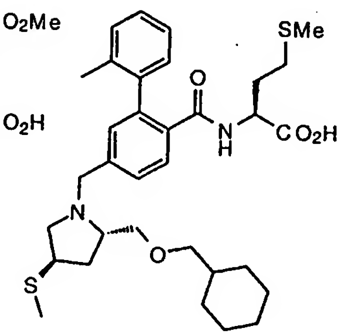

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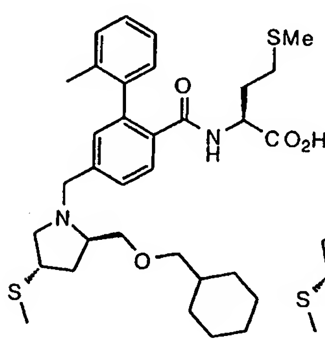
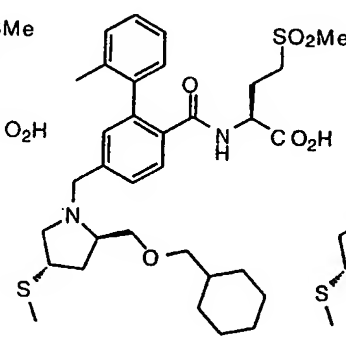
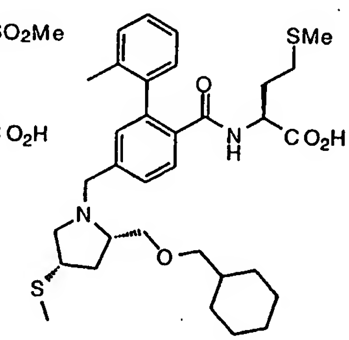

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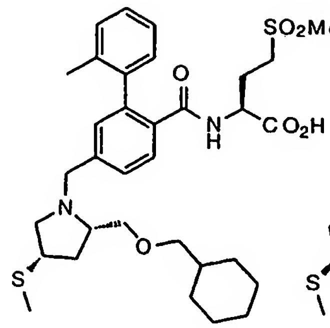 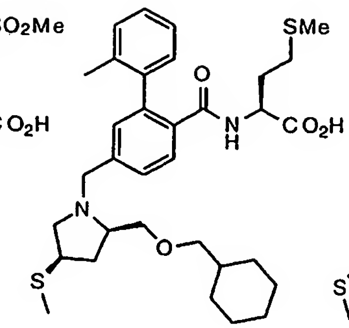 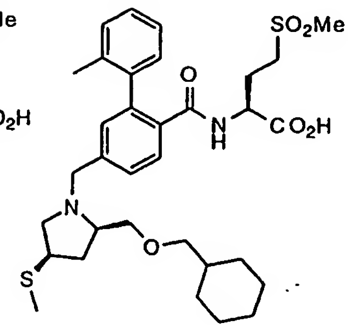

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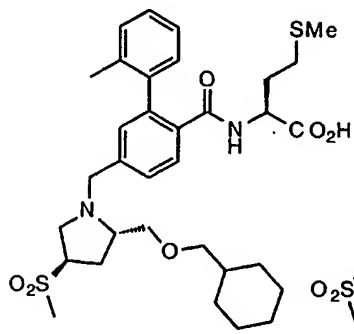 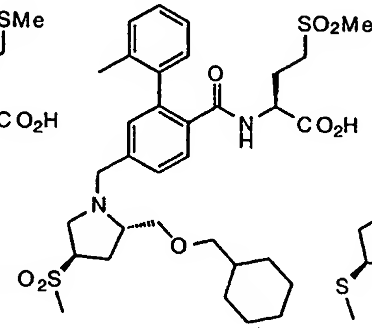 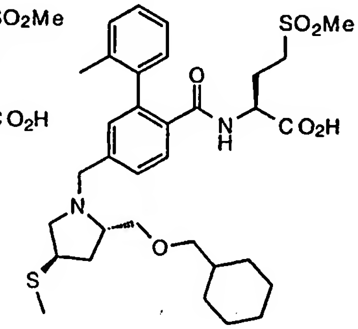

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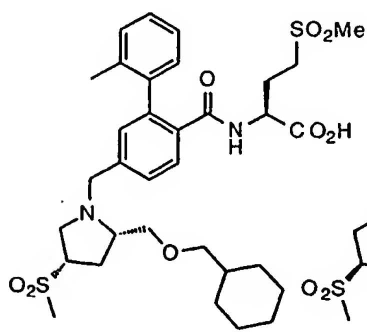 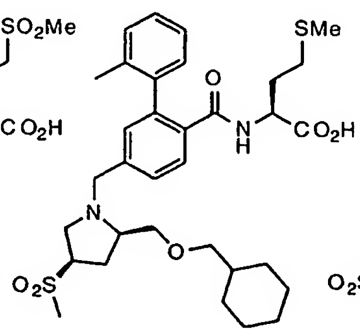 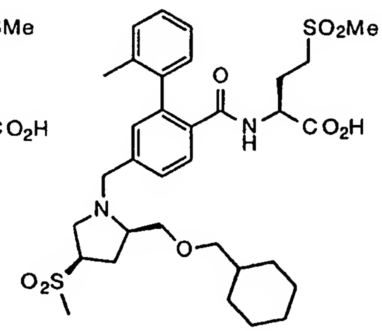

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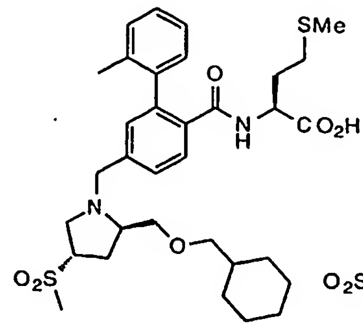
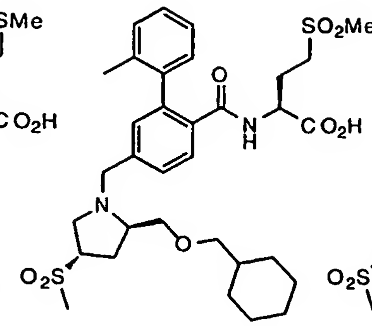
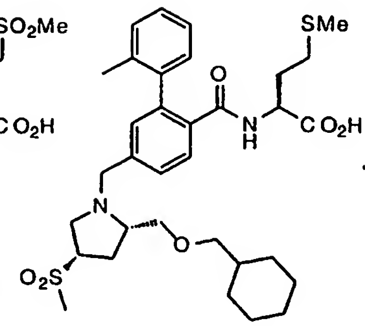

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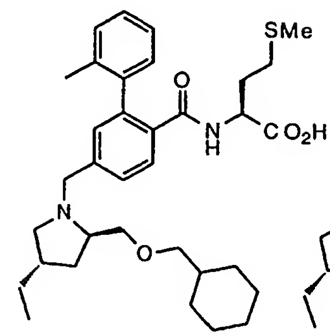
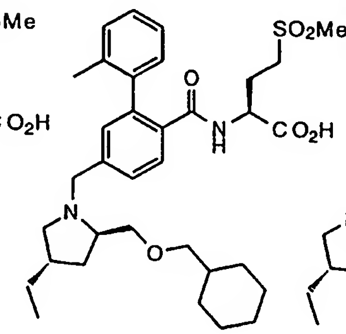
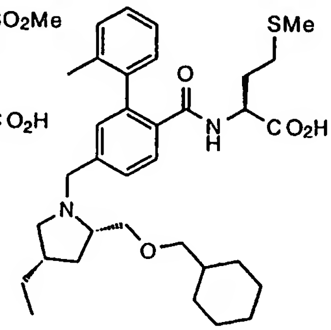

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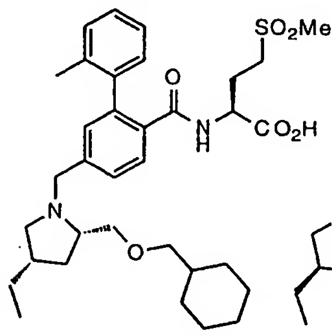
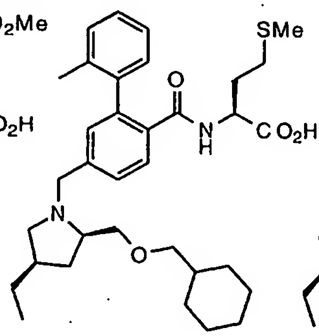
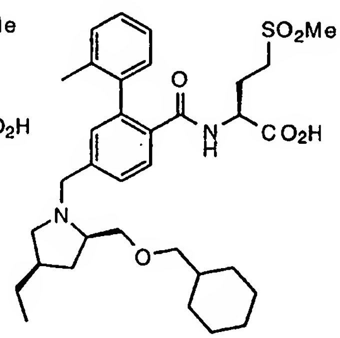

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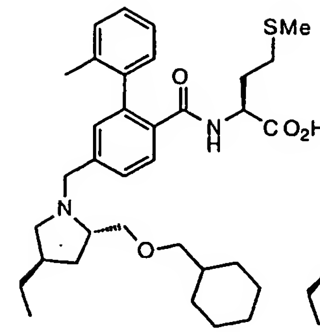 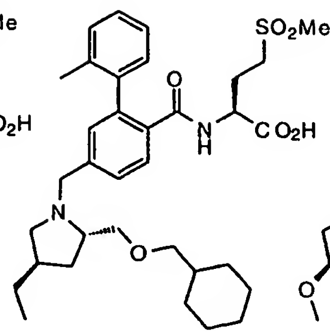 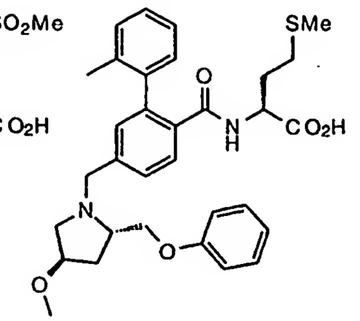

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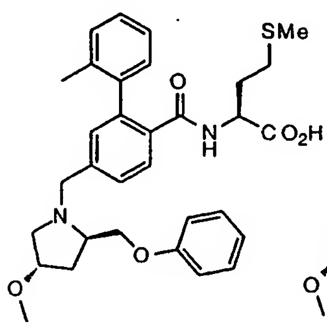 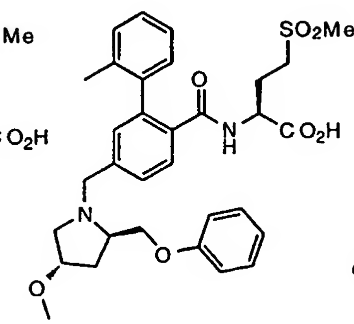 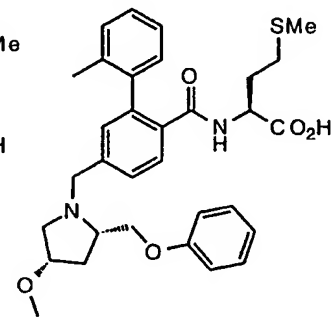

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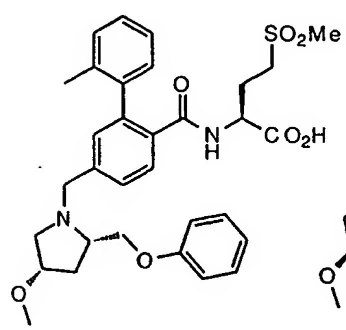 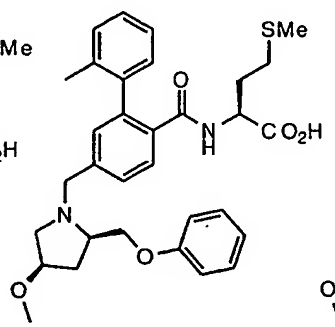 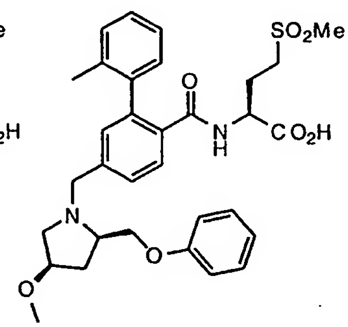

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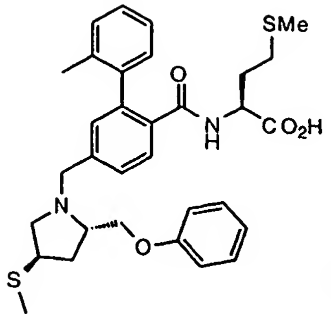
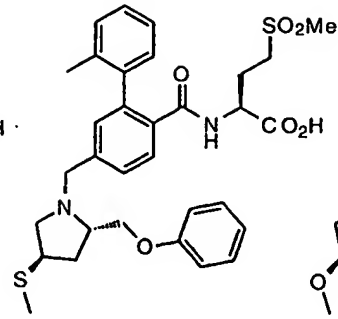
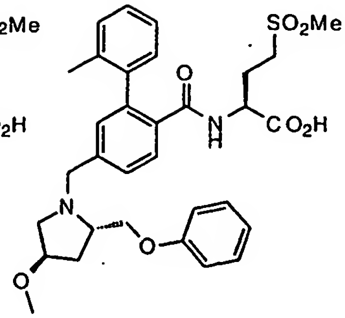

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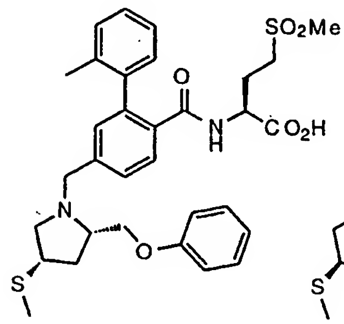
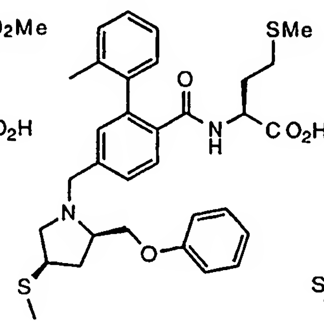
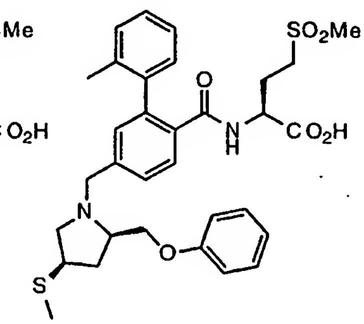

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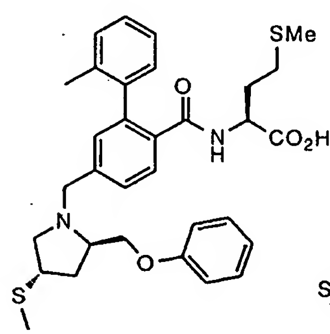
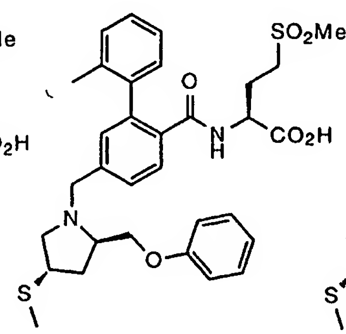
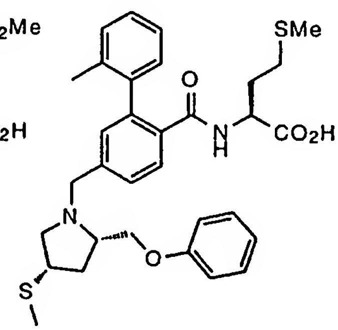

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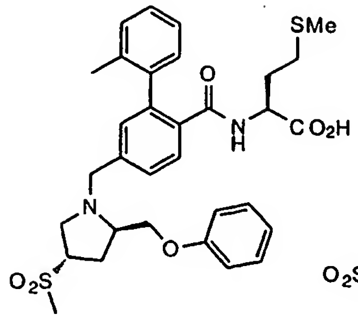
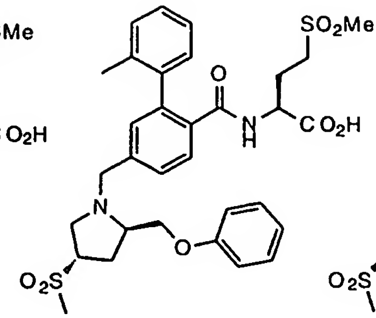
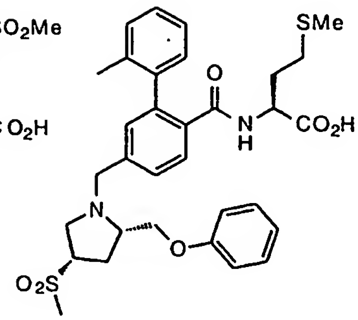

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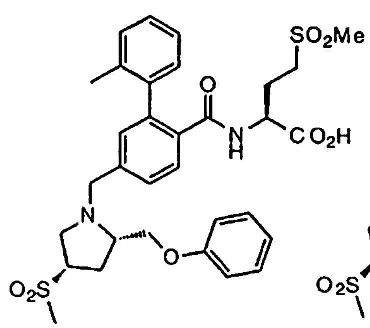
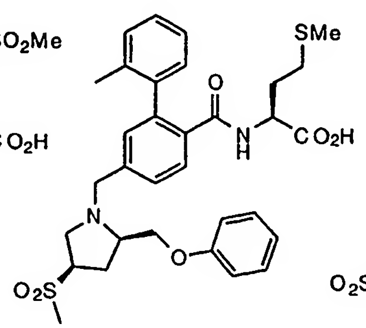
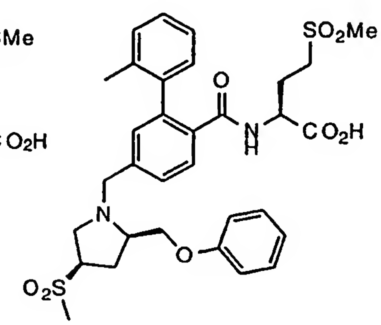

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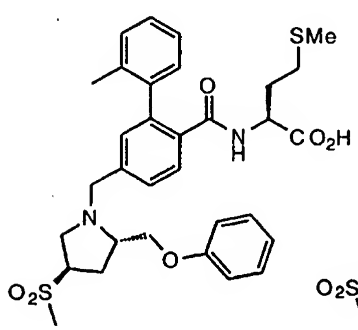
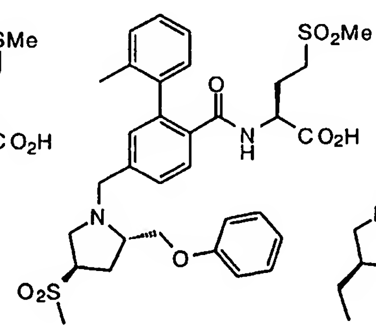
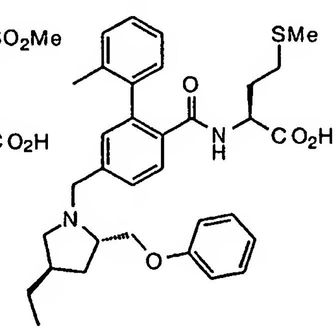

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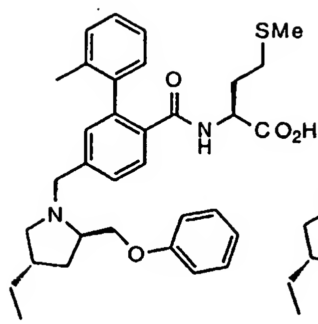 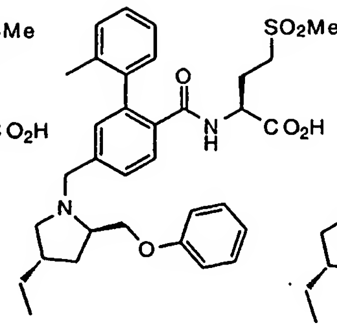 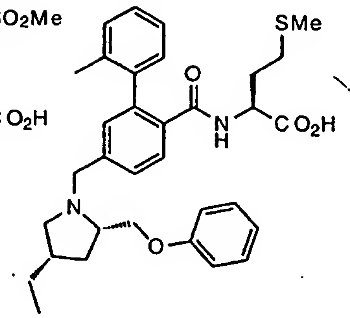

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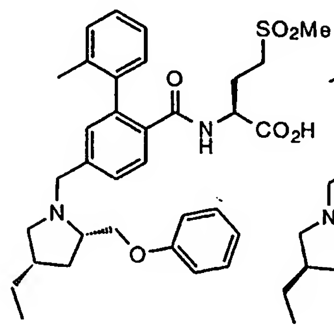 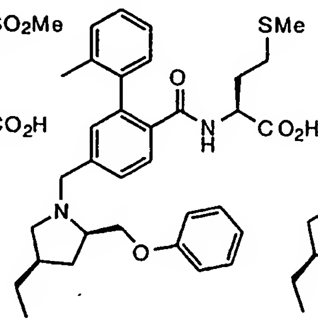 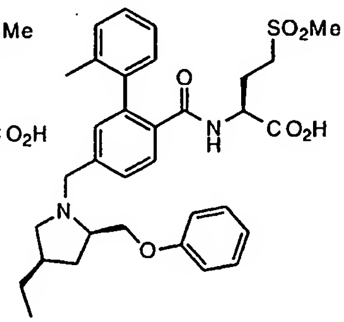

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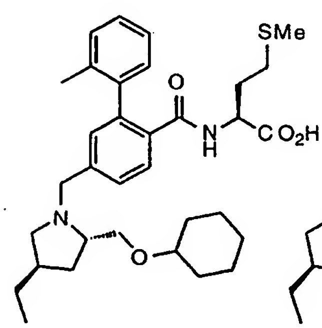 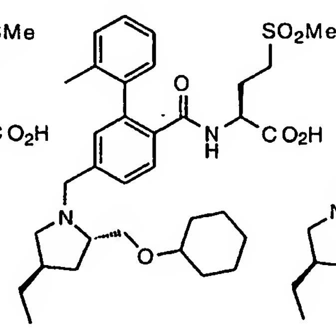 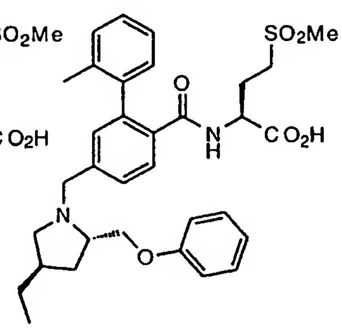

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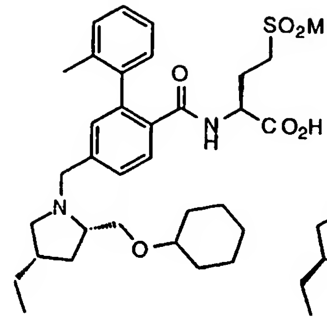 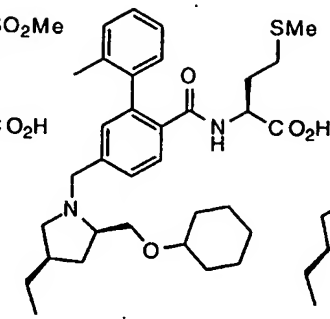 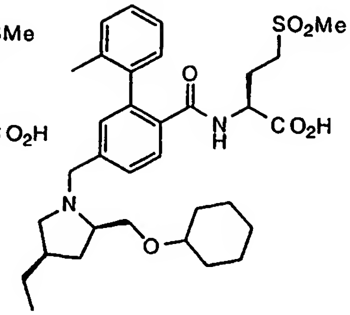

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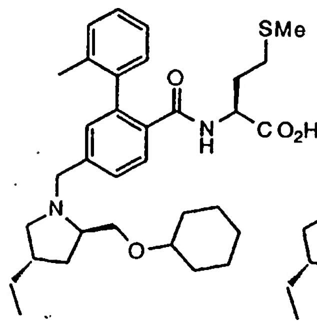 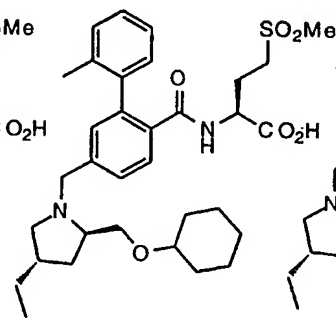 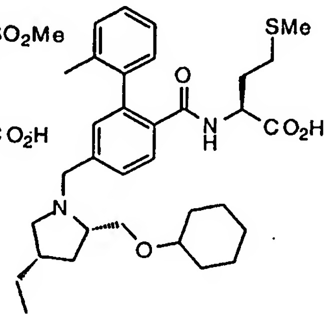

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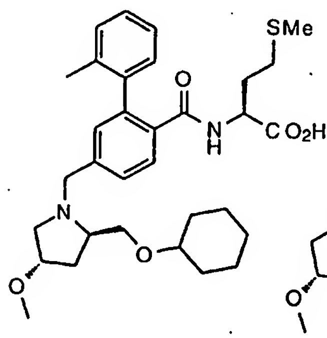 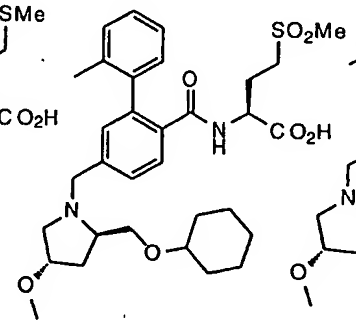 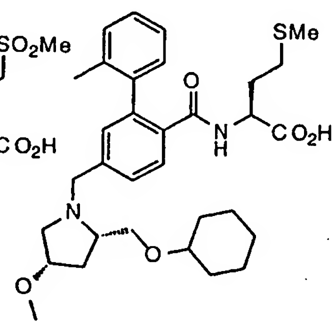

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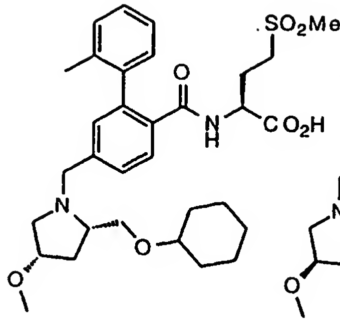
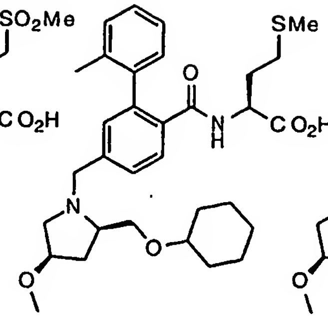
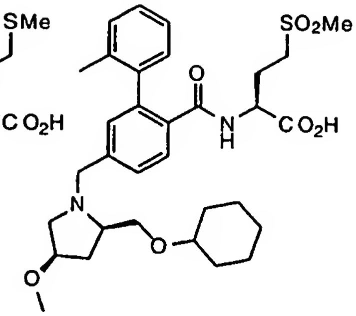

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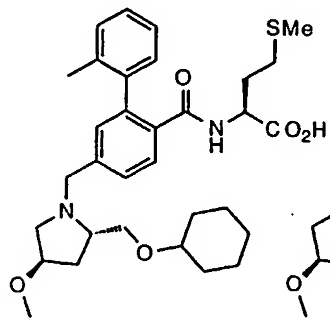
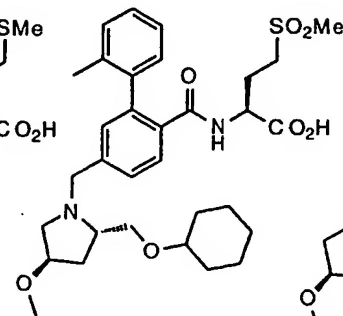
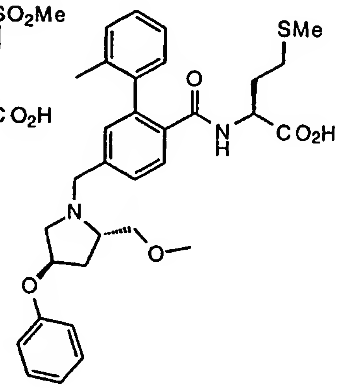

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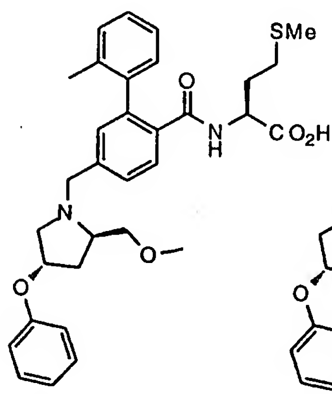
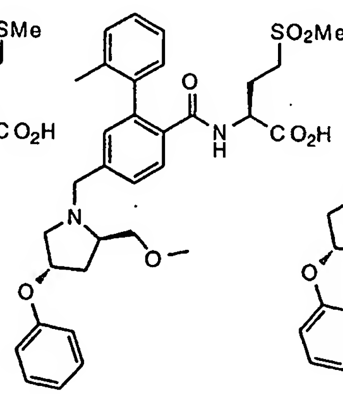
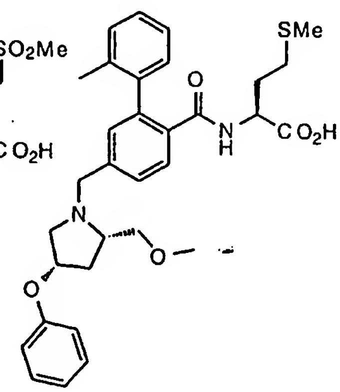

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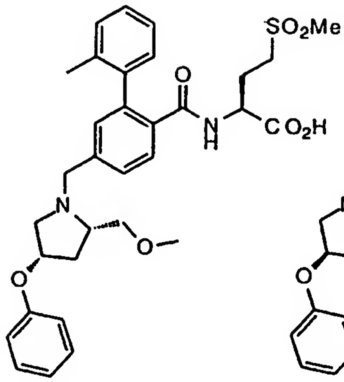

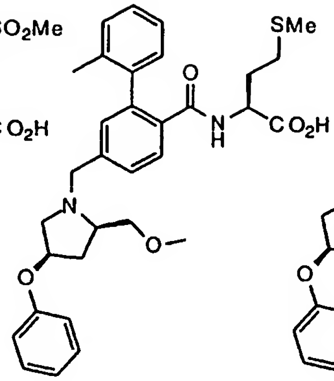

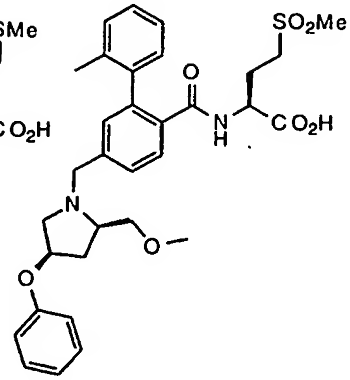

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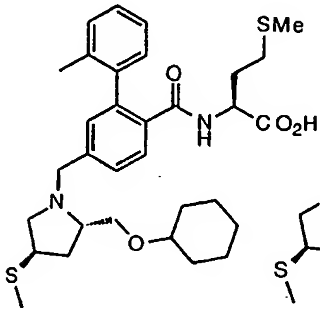

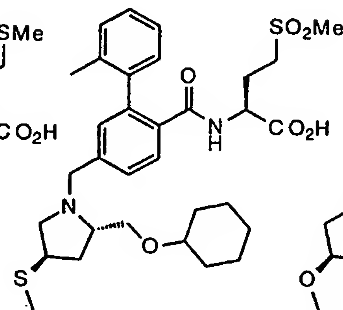

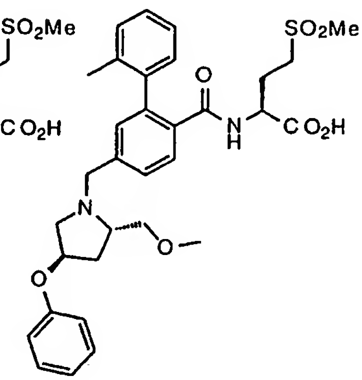

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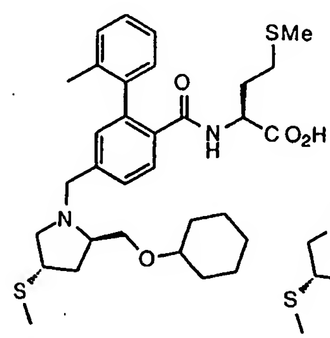

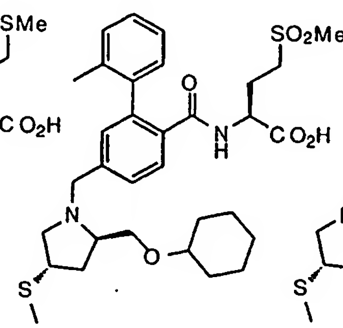

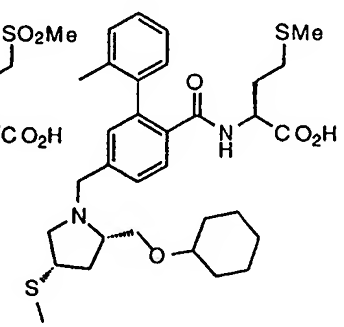

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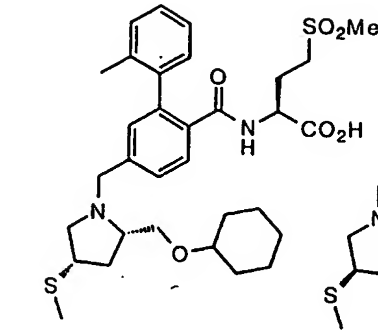
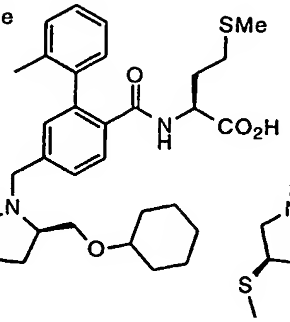
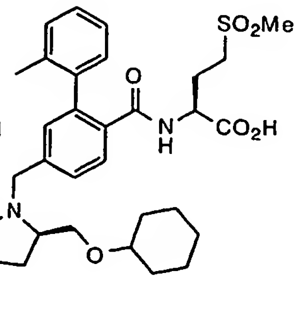

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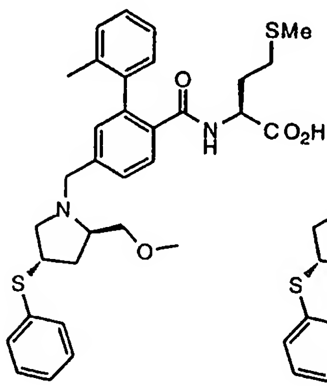
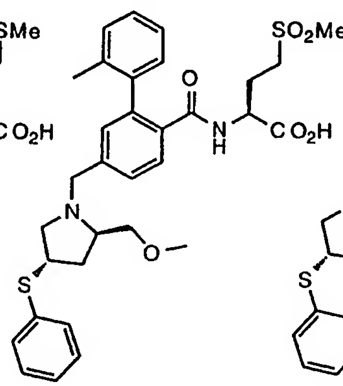
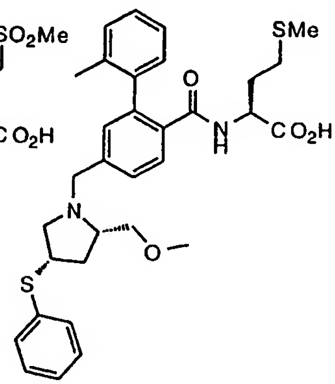

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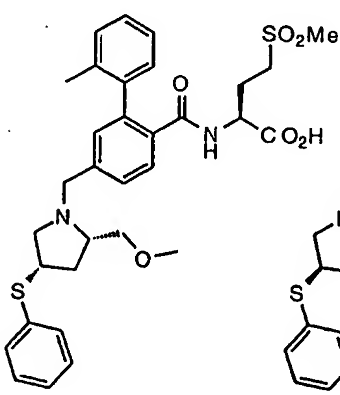
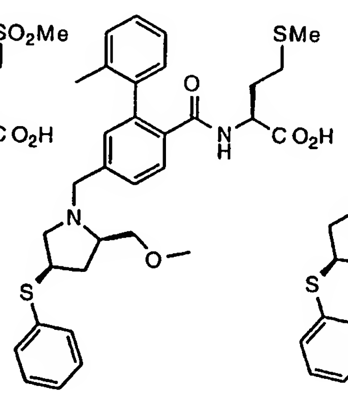
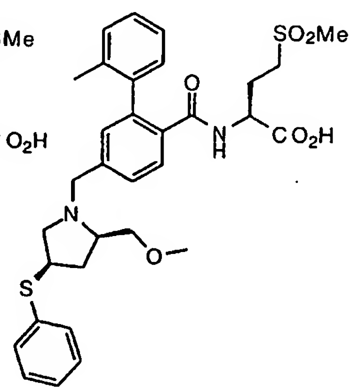

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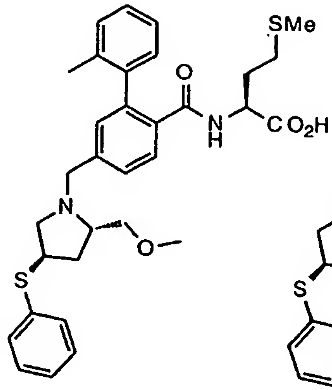
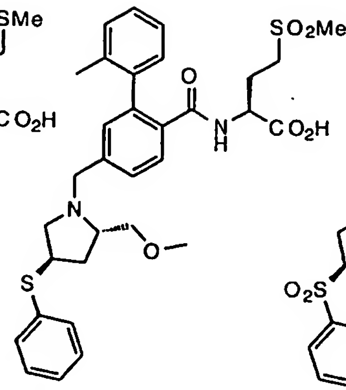
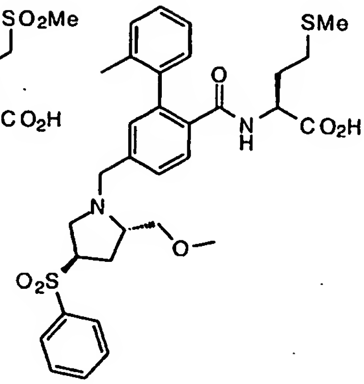

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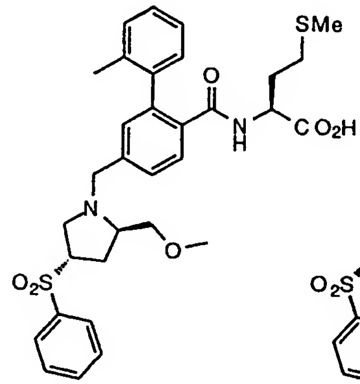
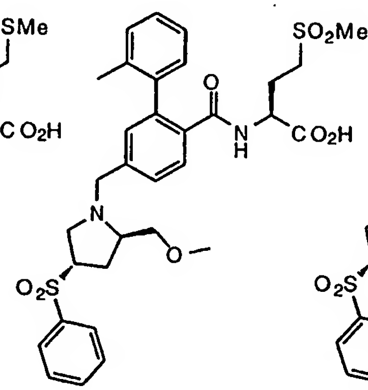
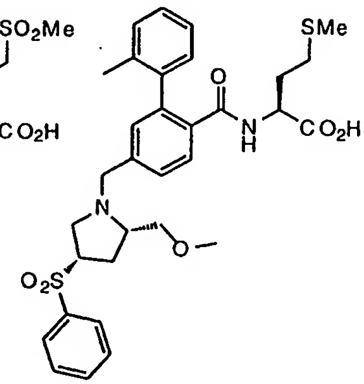

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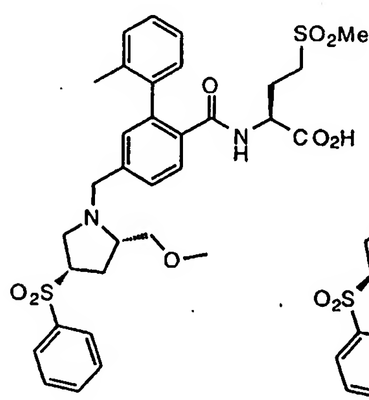
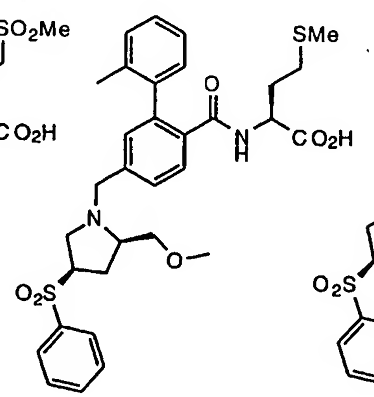
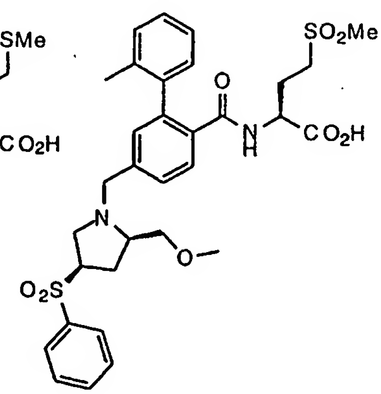

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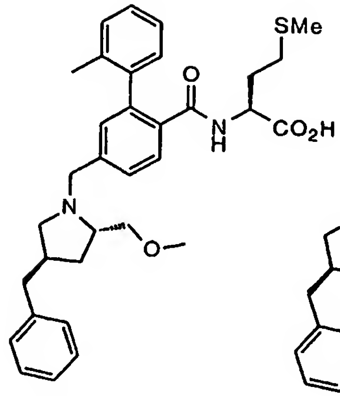
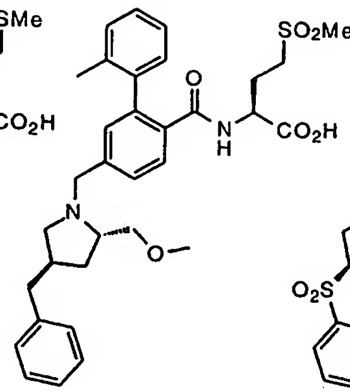
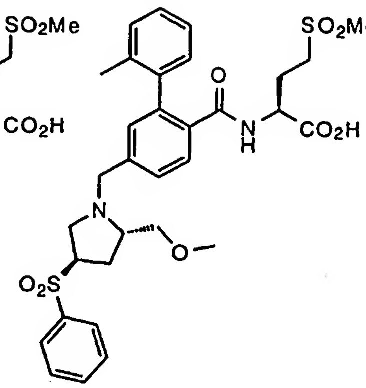

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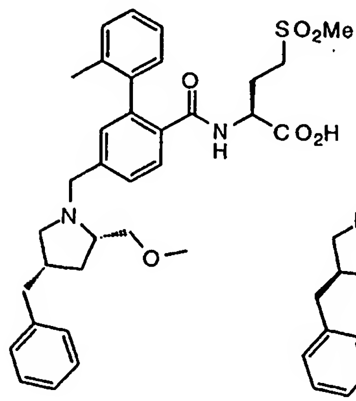
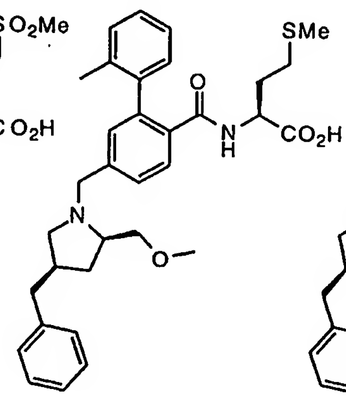
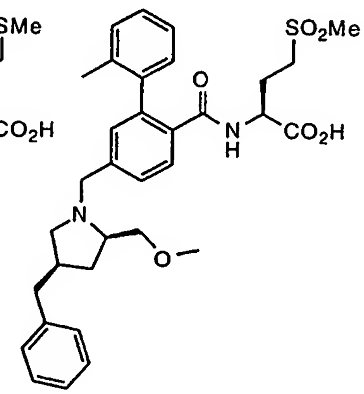

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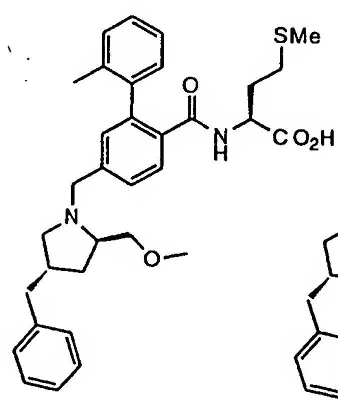
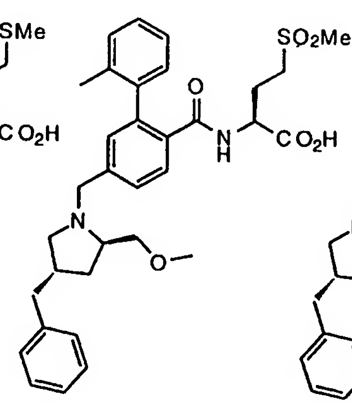
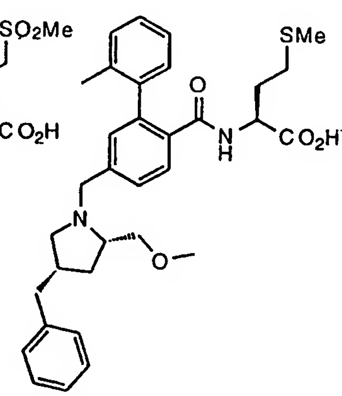

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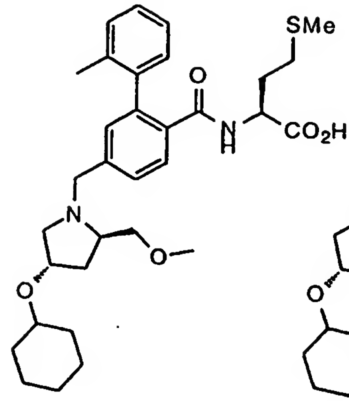 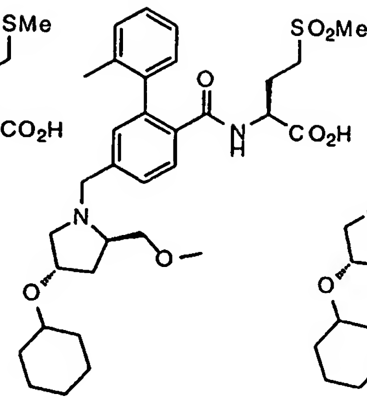 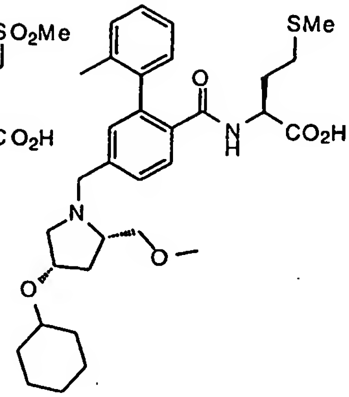

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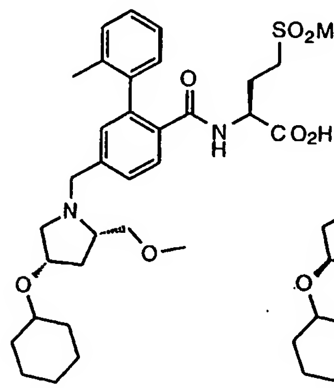 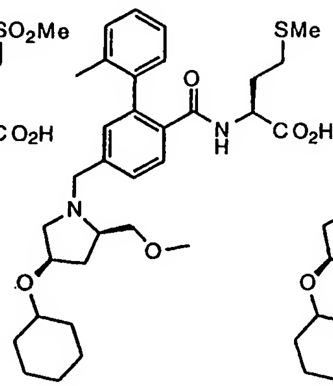 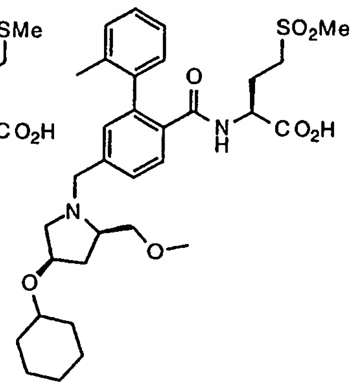

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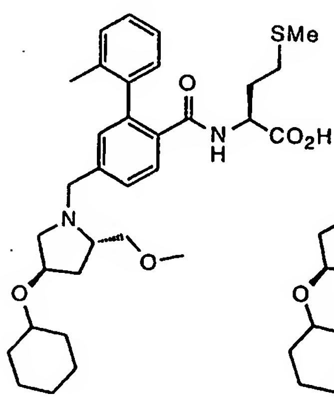 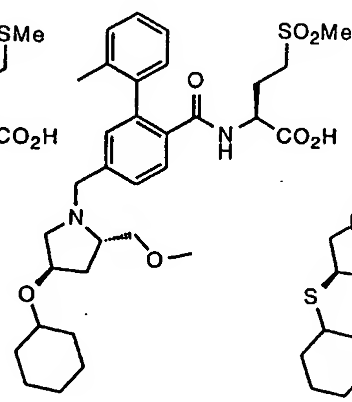 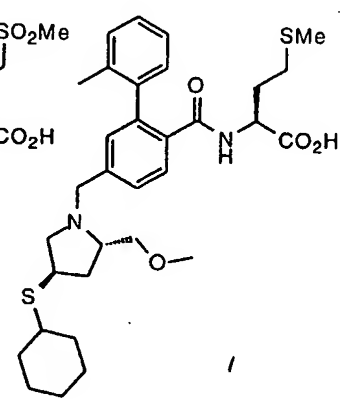

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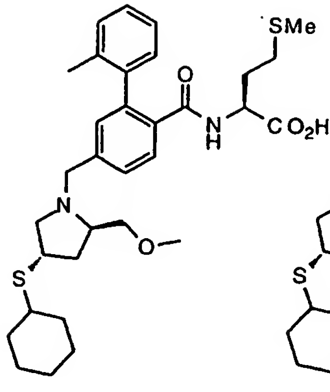 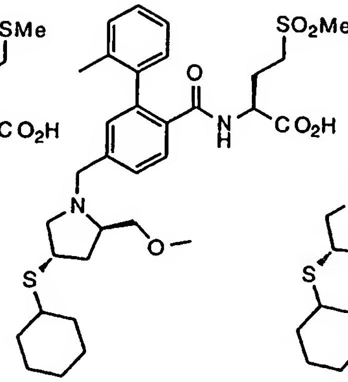 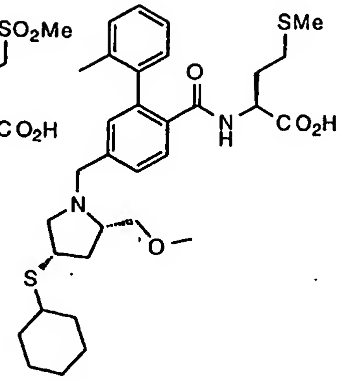

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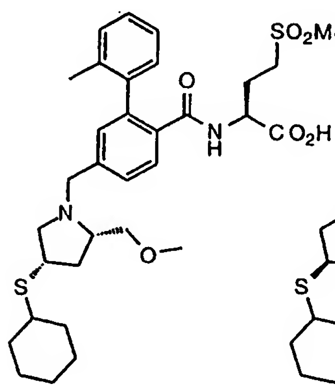 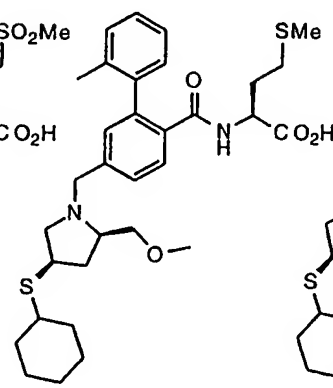 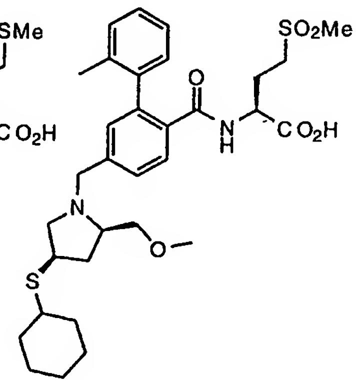

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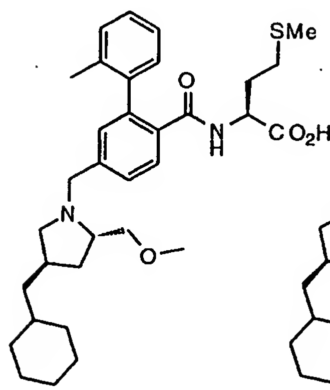 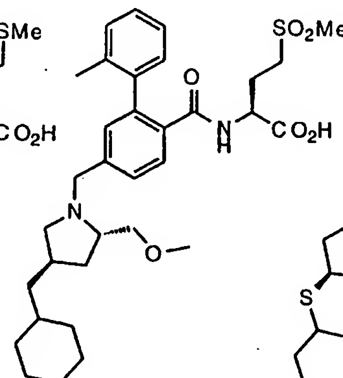 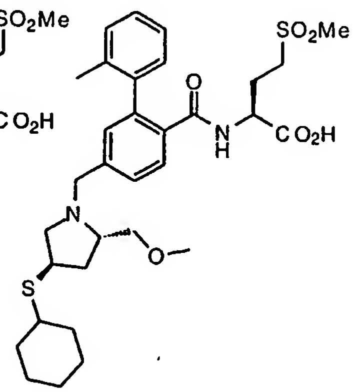

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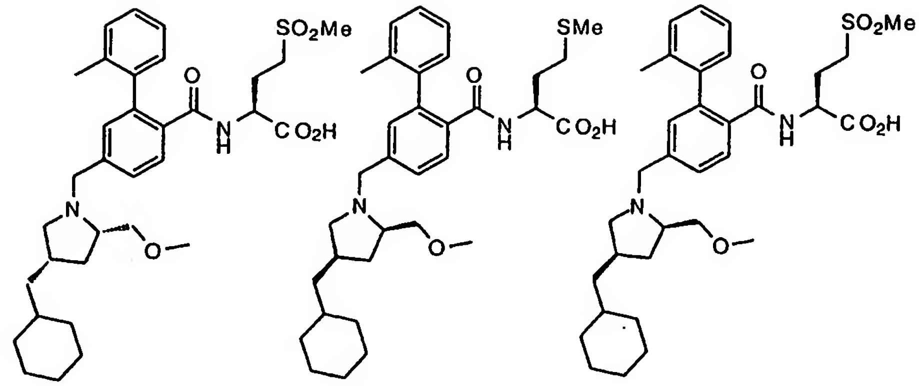

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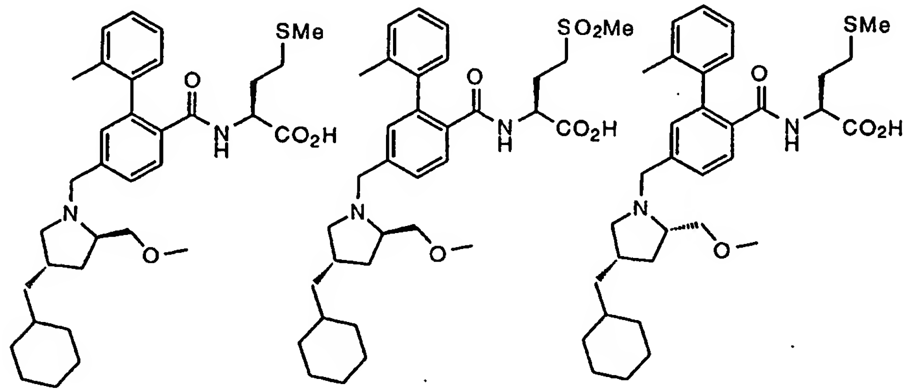

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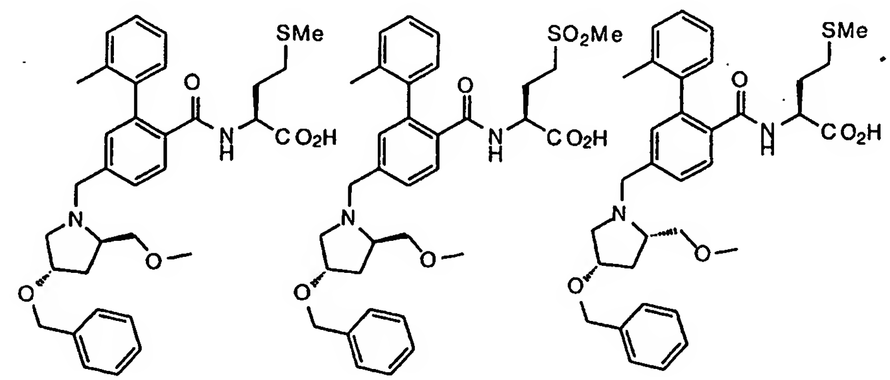

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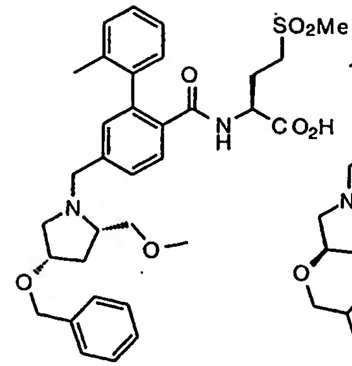
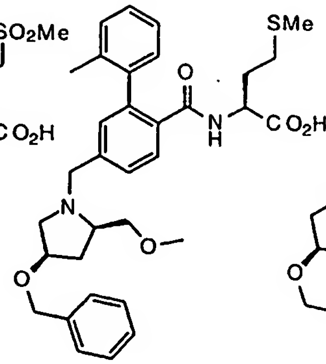
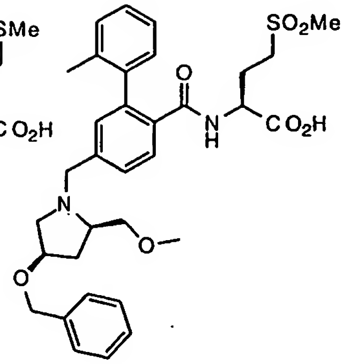

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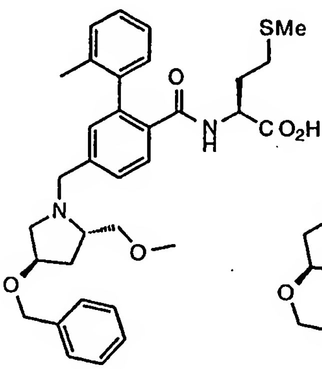
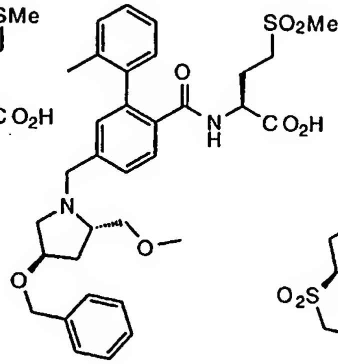
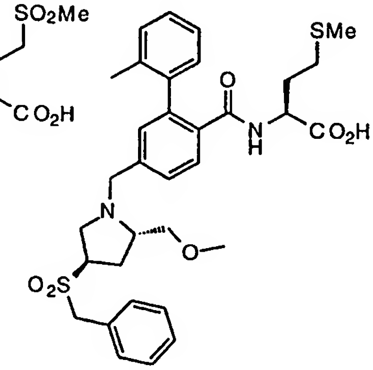

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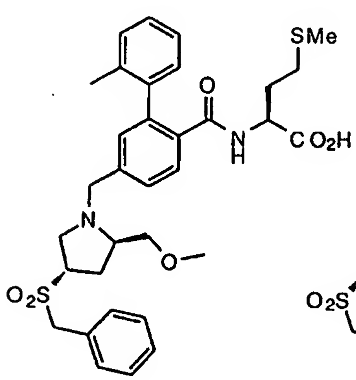
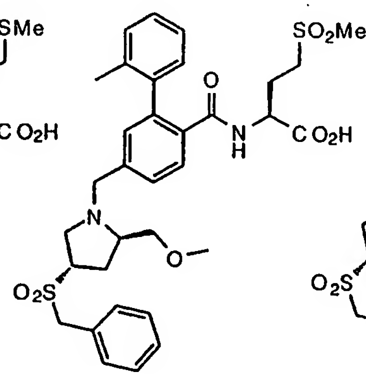
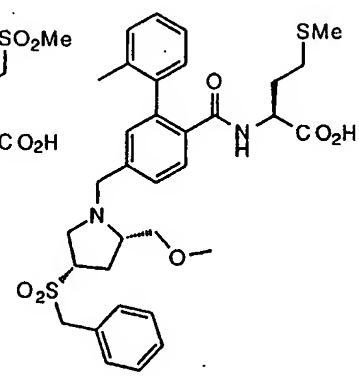

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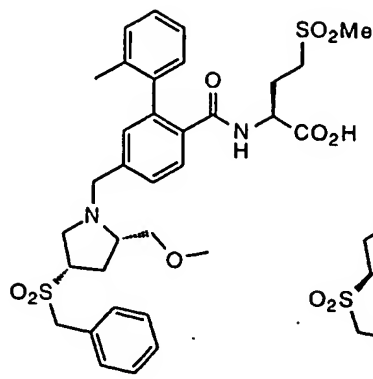
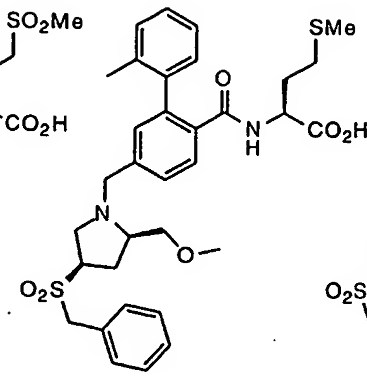
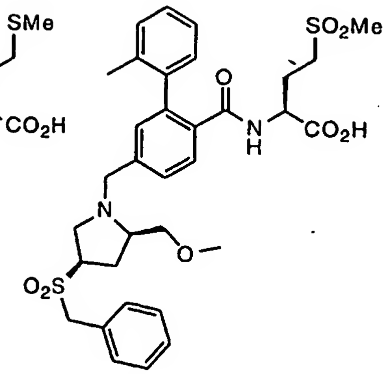

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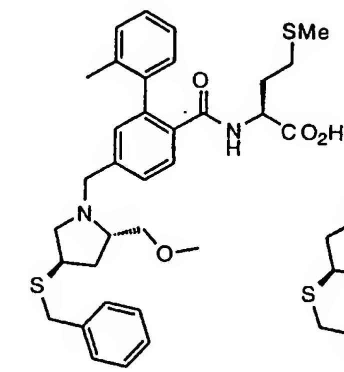
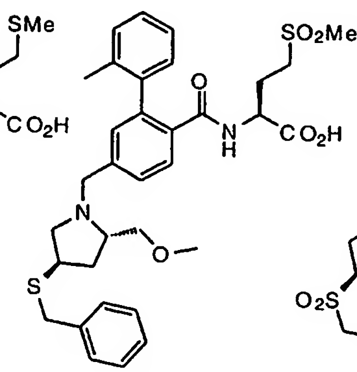
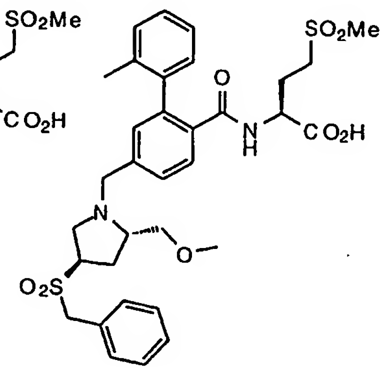

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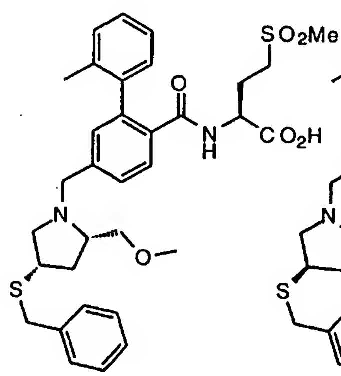
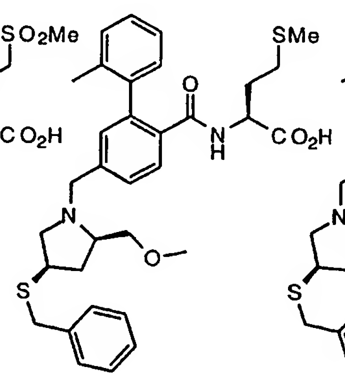
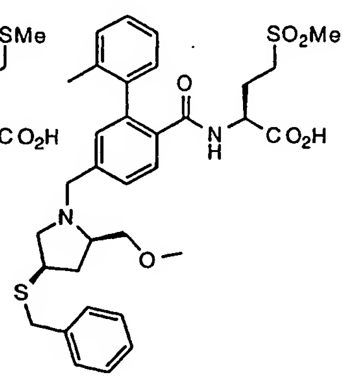

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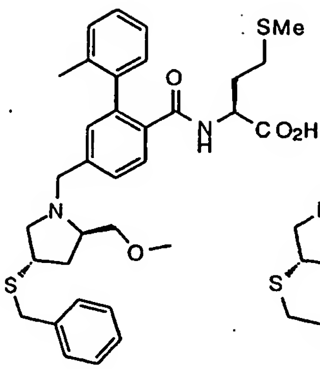

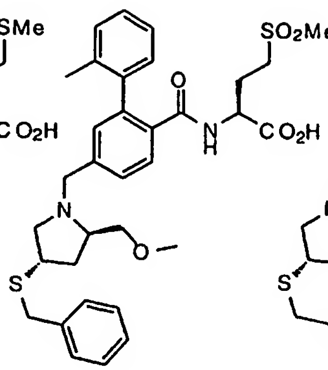

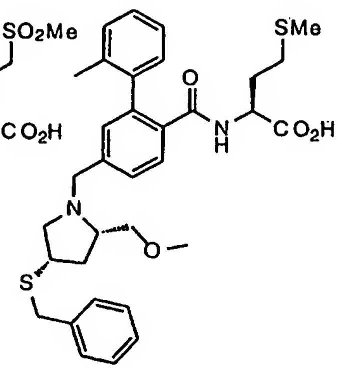

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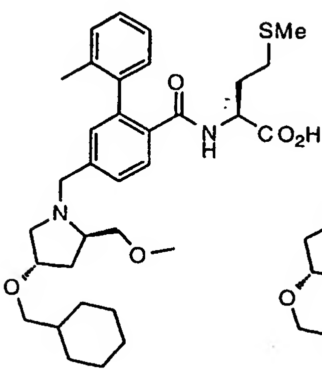

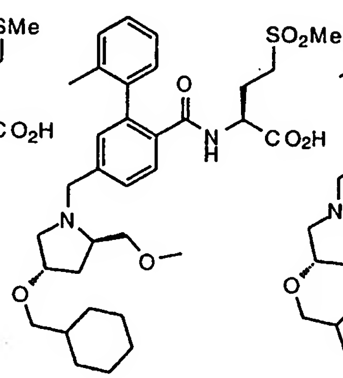

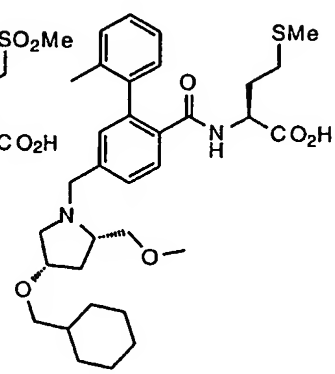

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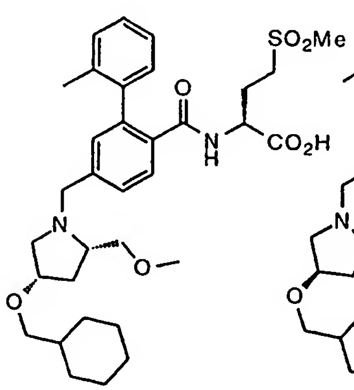

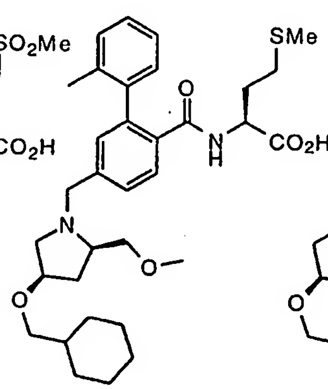

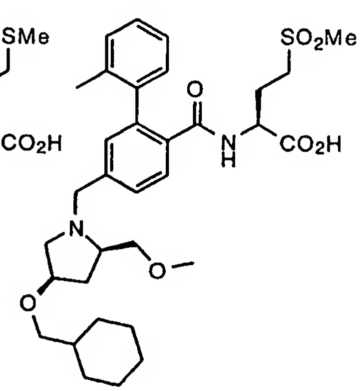

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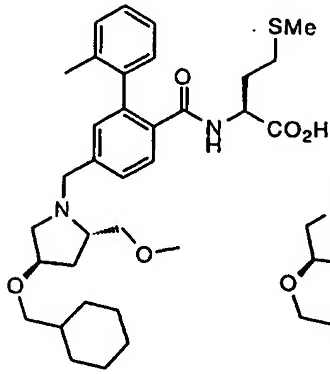
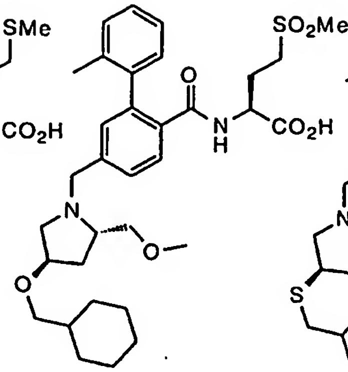
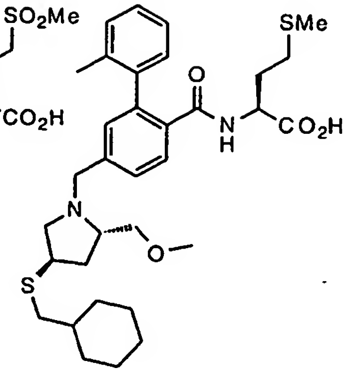

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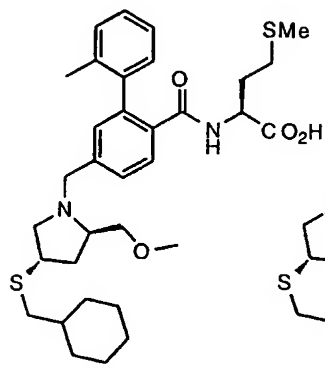
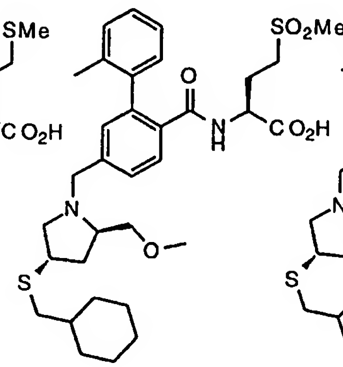
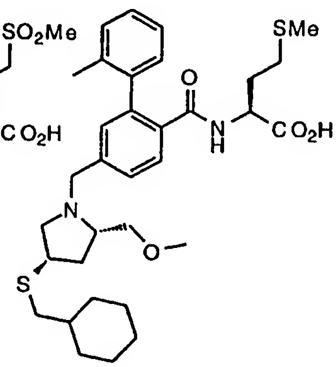

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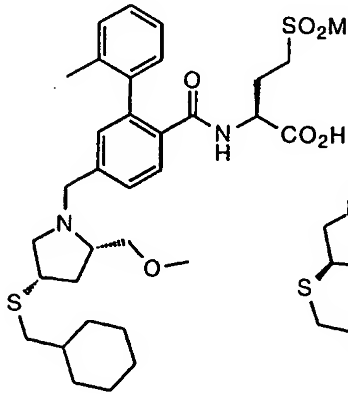
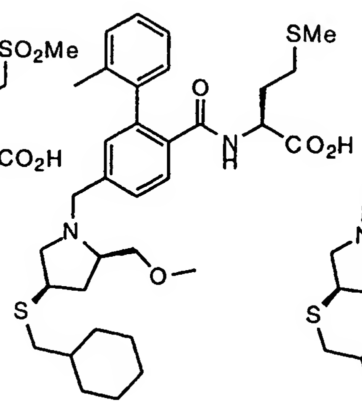
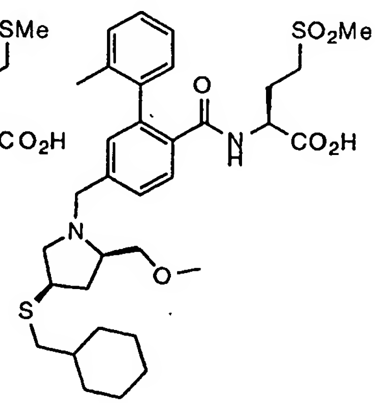

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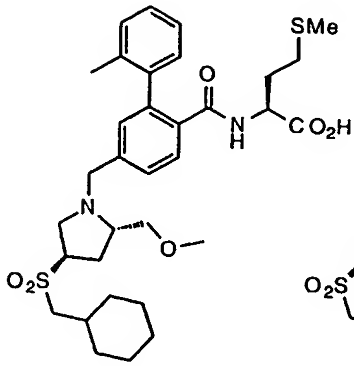

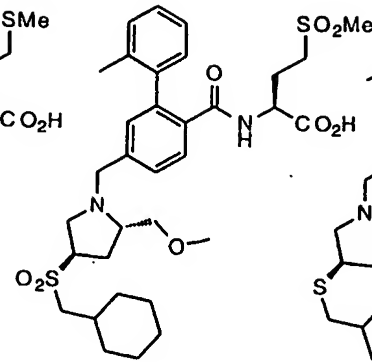

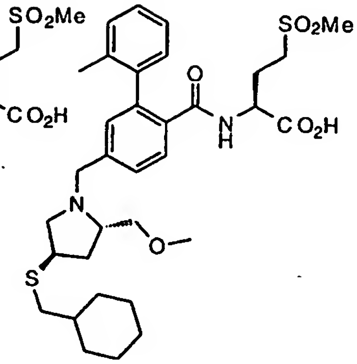

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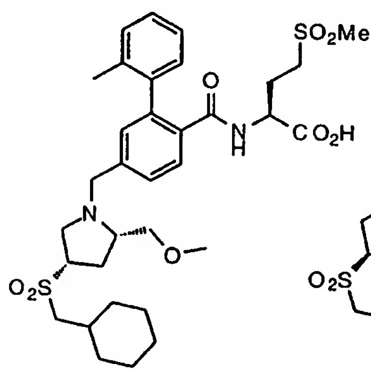

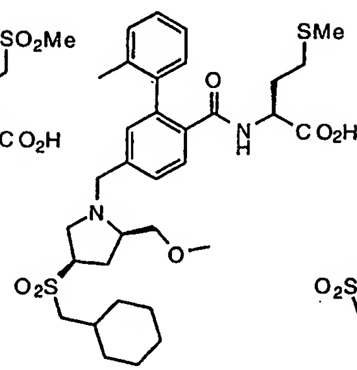

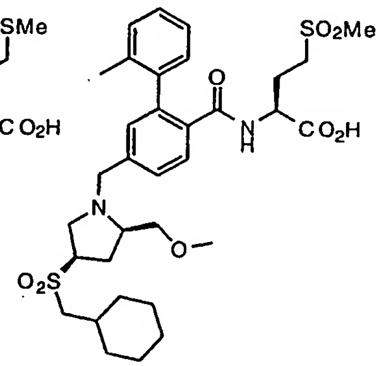

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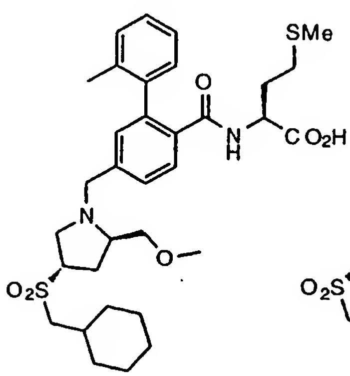

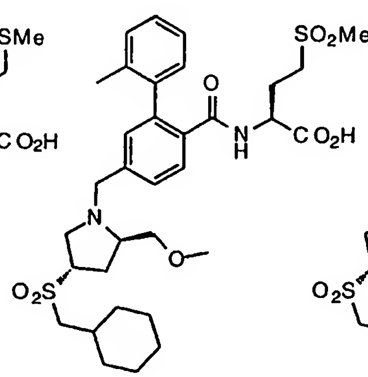

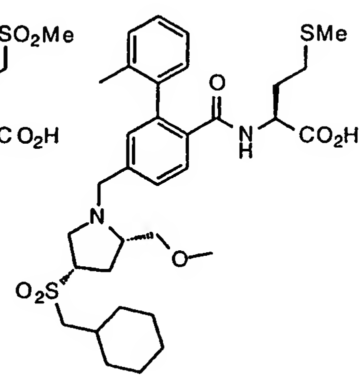

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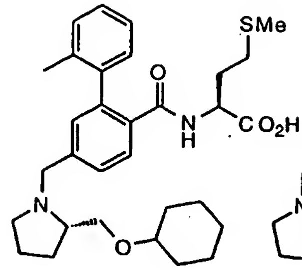
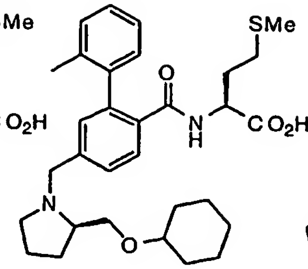
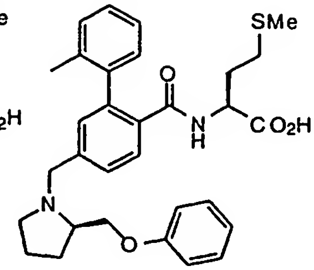

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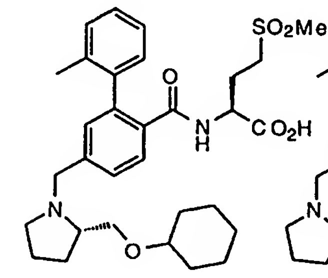
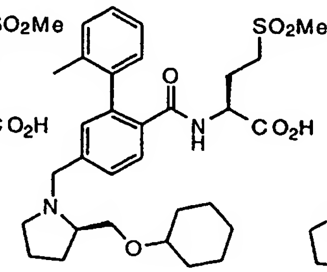
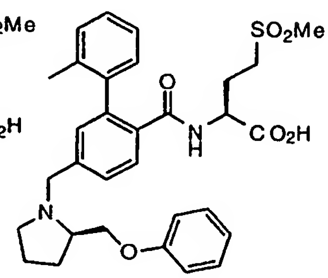

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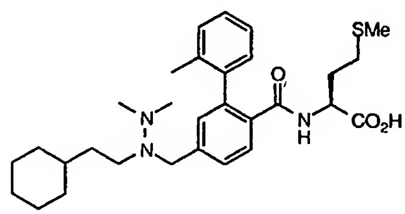
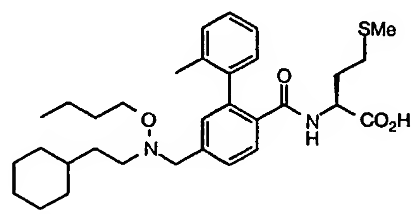

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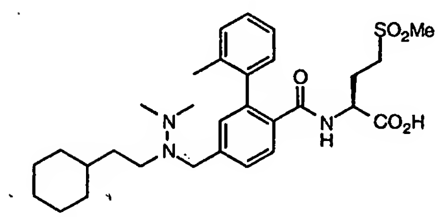
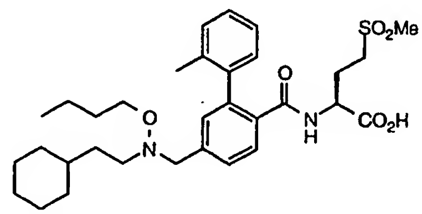

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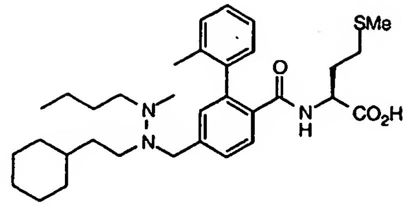
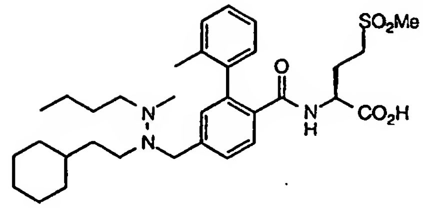

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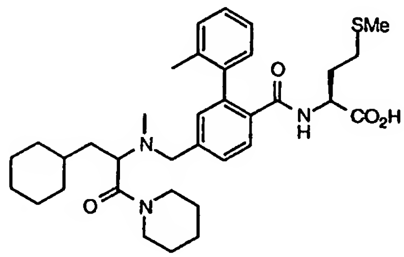
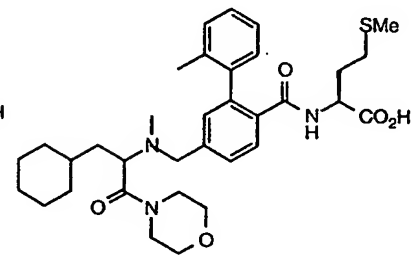

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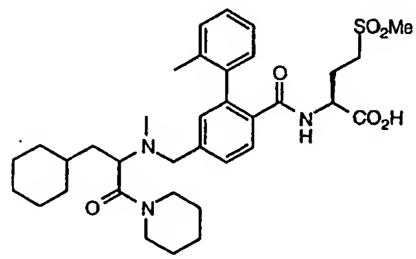
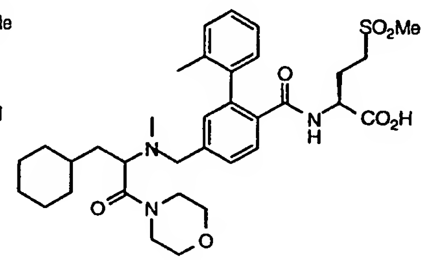

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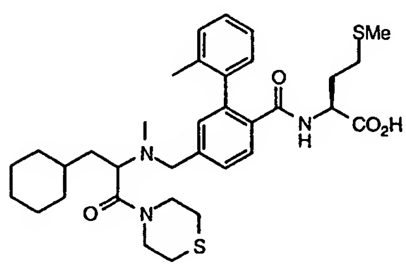
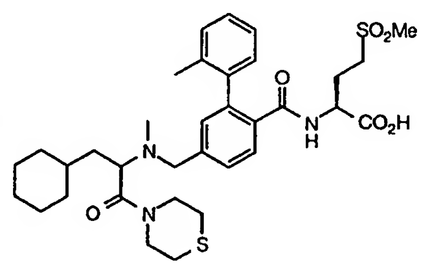

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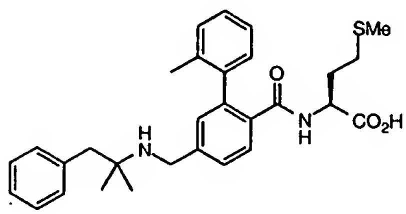
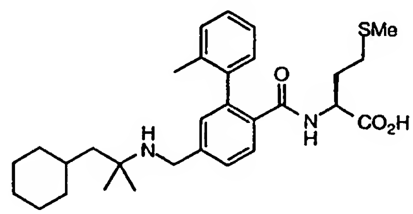

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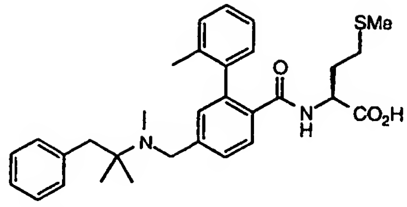

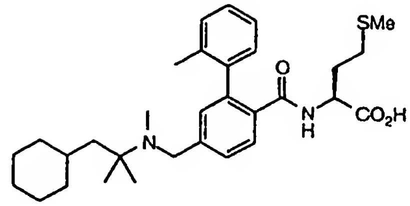

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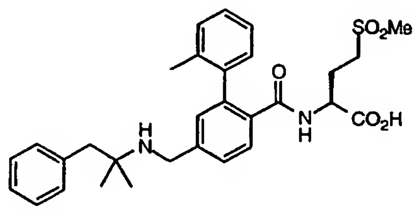

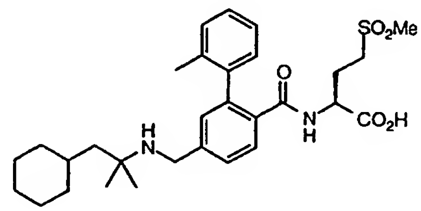

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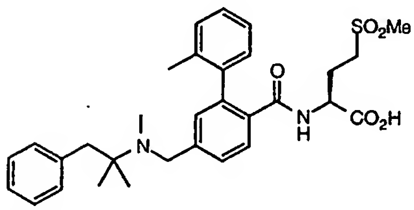

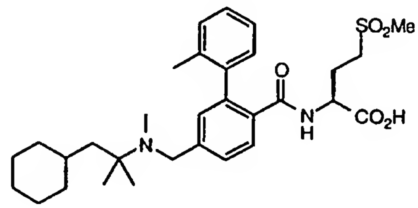

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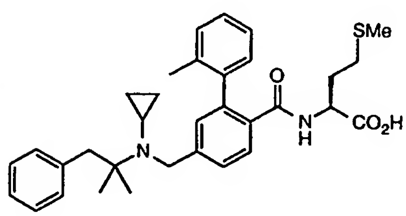

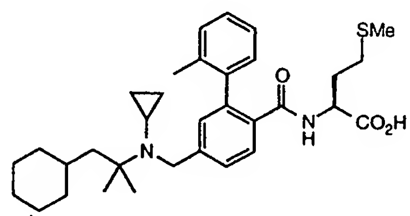

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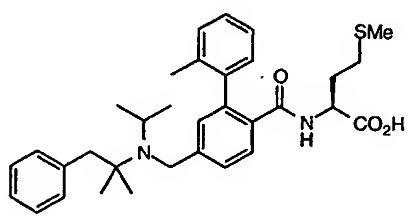

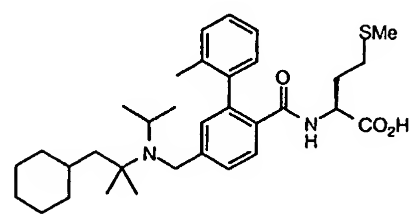

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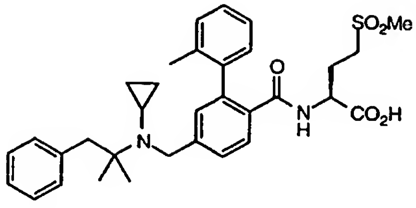

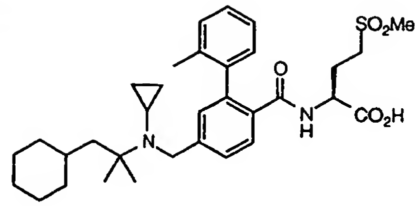

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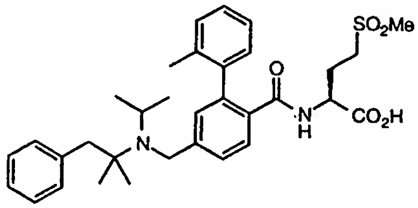

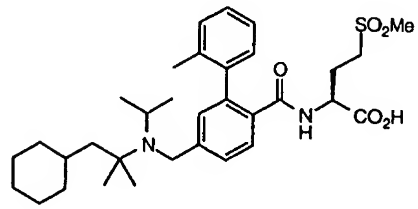

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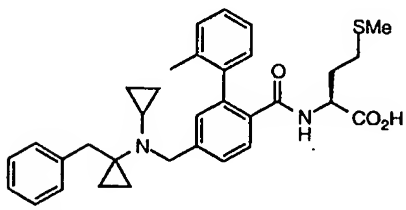

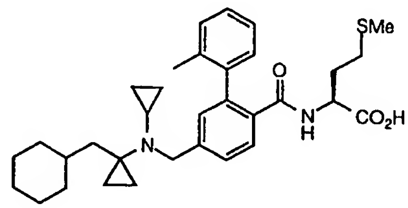

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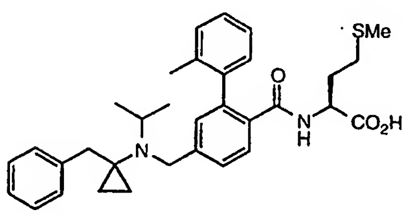

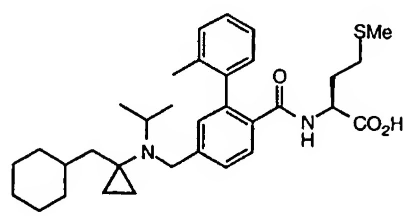

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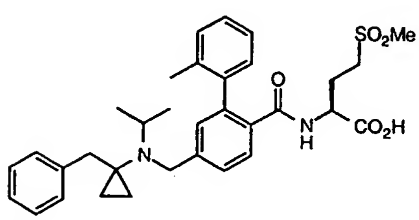

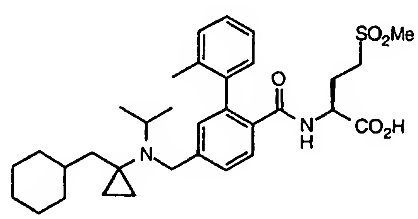

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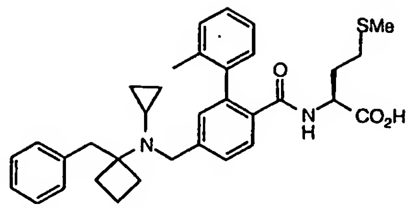

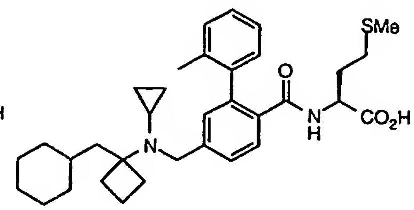

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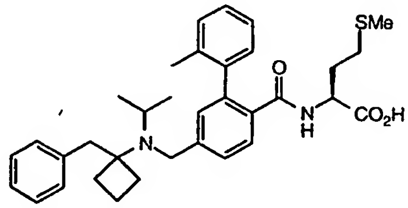

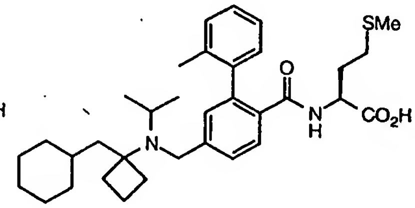

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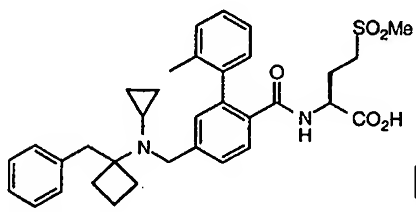

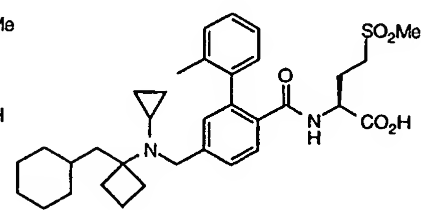

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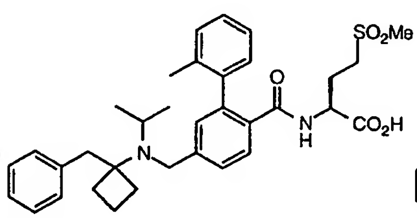

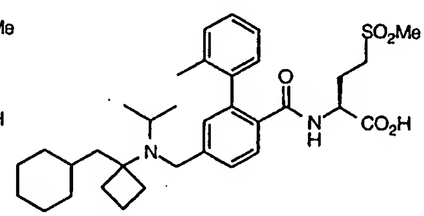

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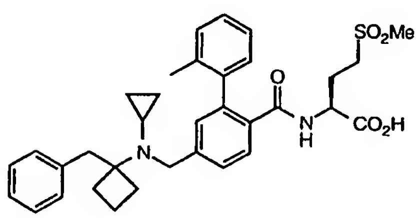

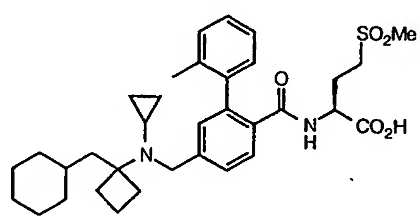

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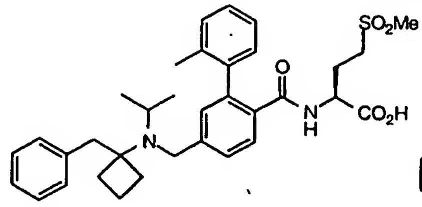
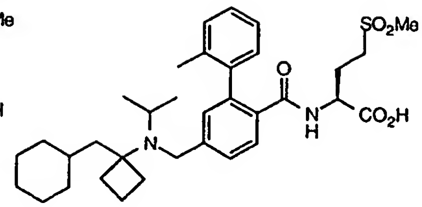

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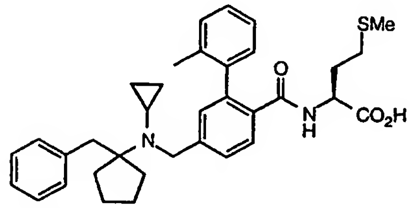
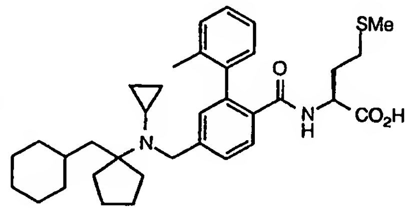

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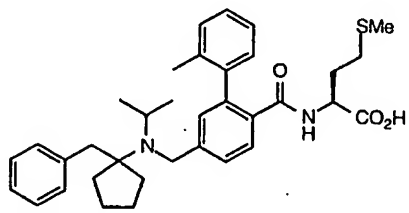
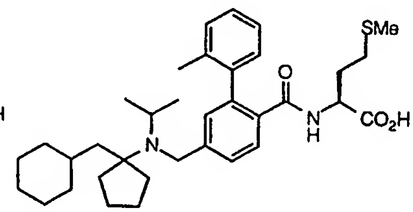

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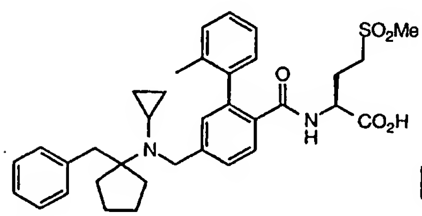
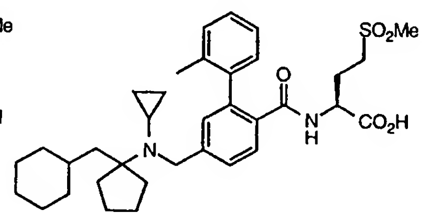

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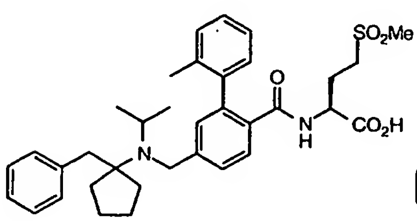
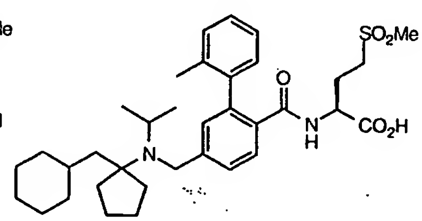

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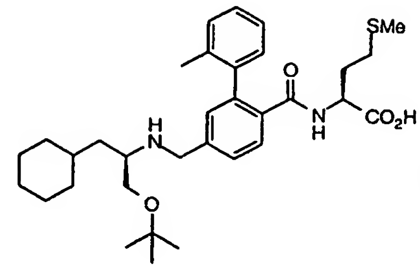
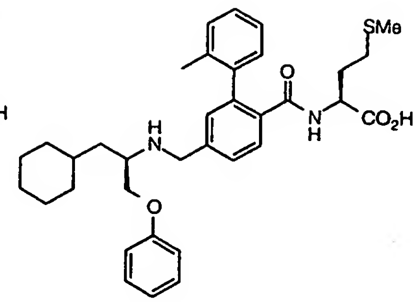

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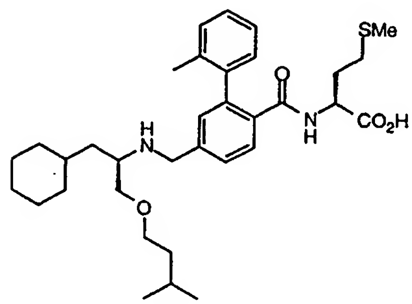
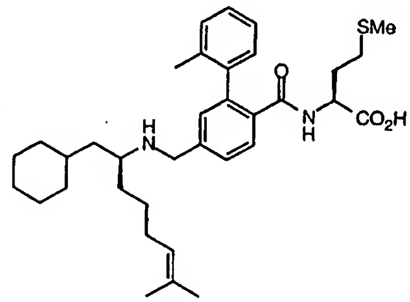

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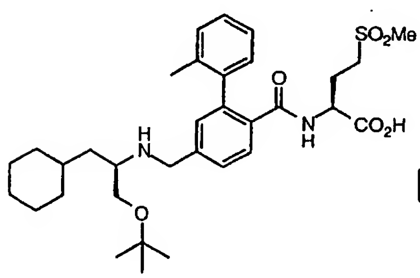
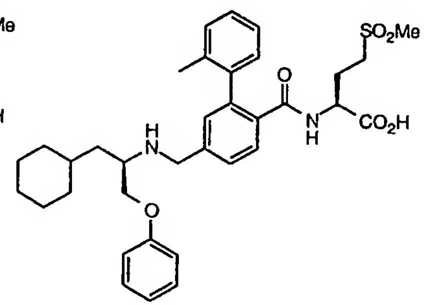

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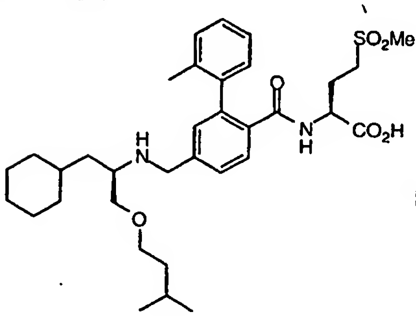
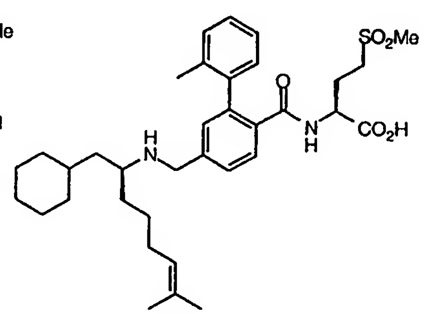

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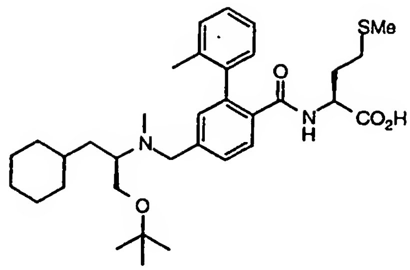

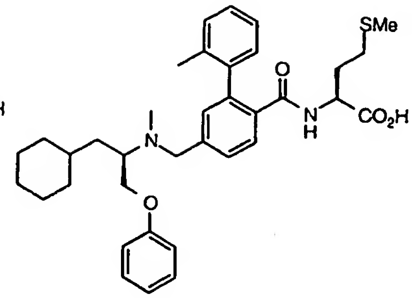

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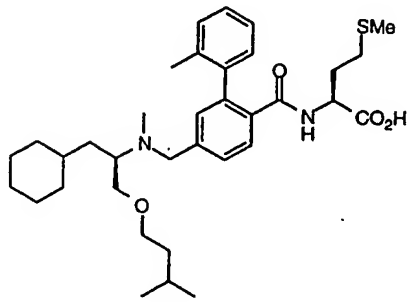

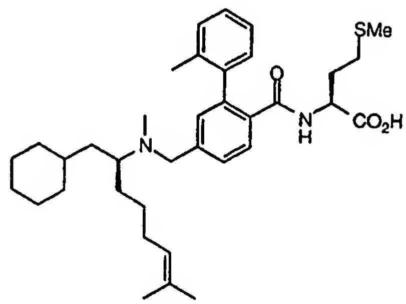

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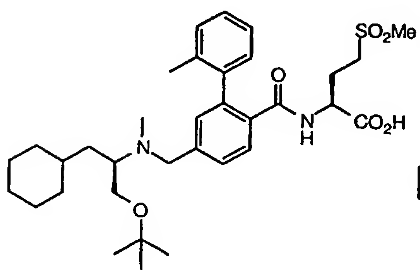

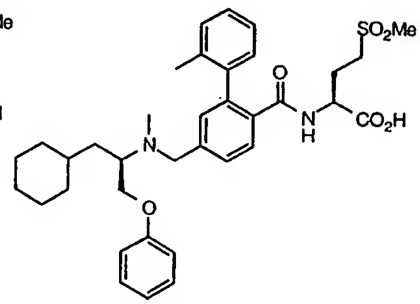

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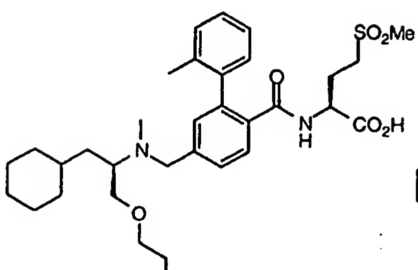

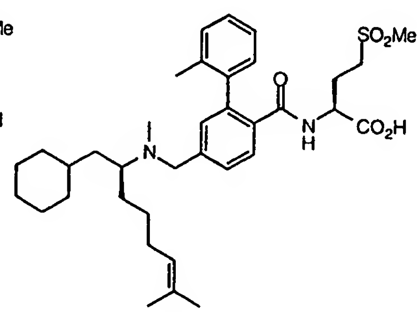

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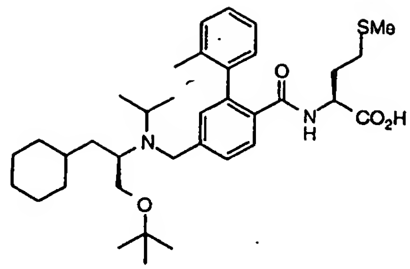

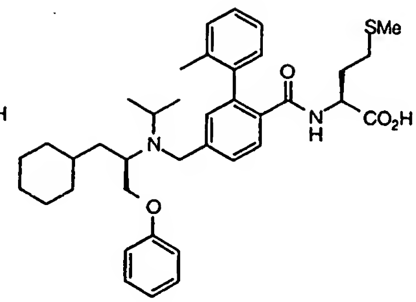

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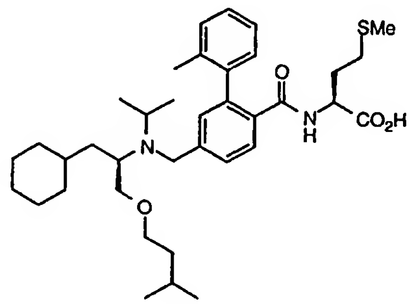

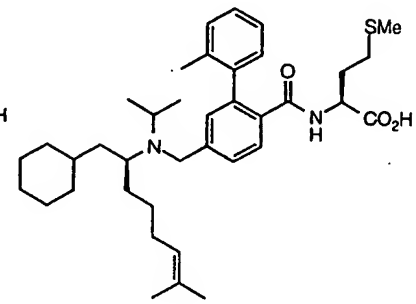

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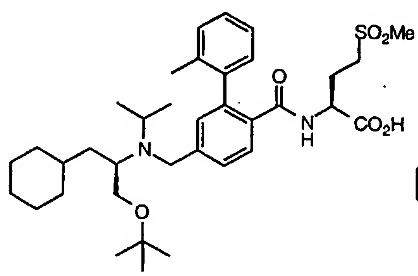

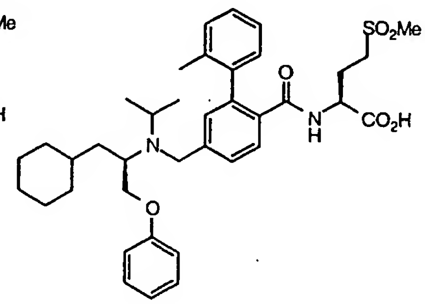

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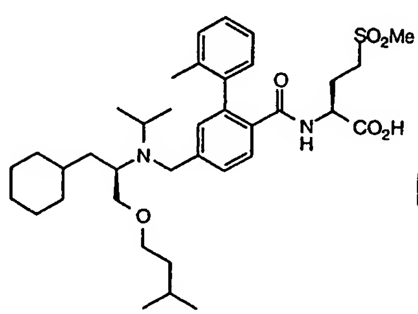

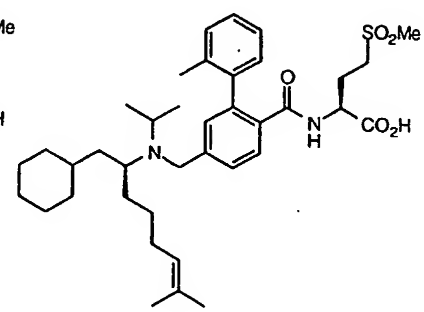

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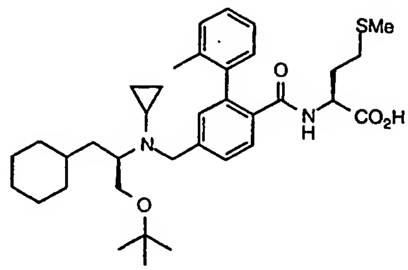
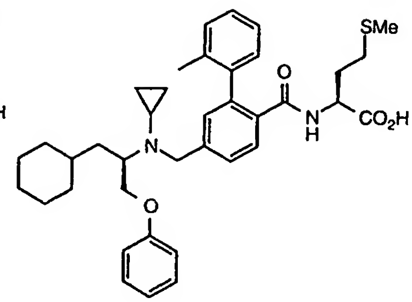

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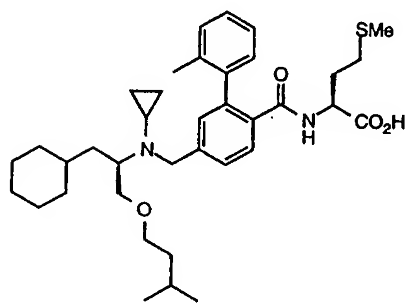
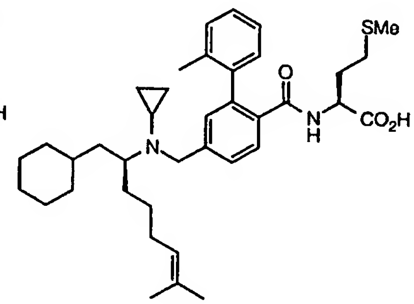

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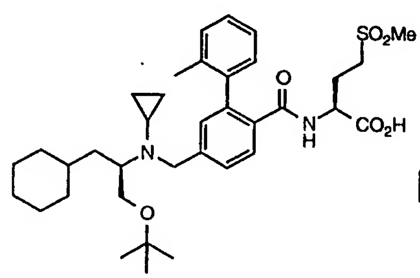
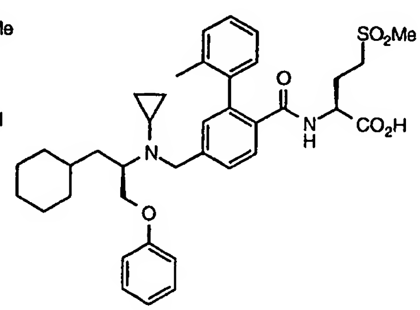

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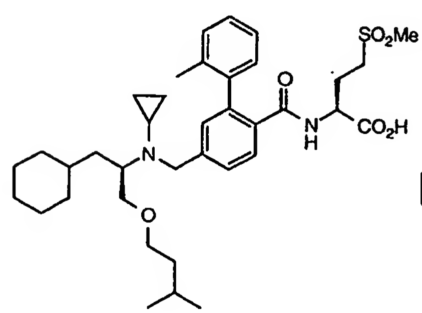
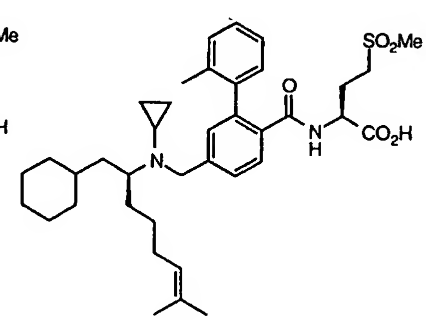

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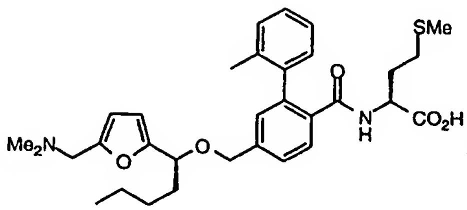
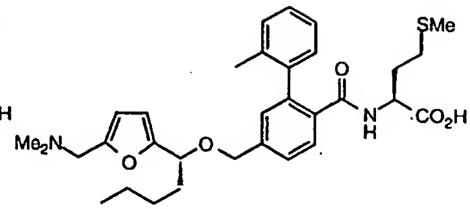
Table 7. Ethers of the Type A-OL_1

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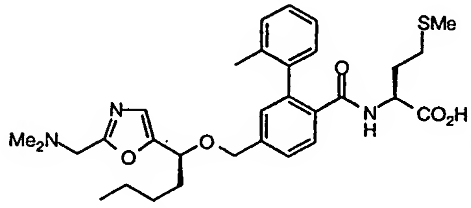
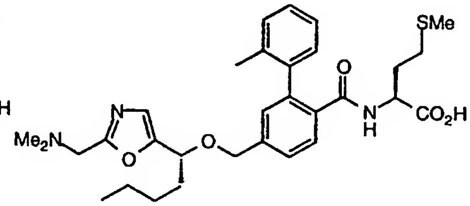

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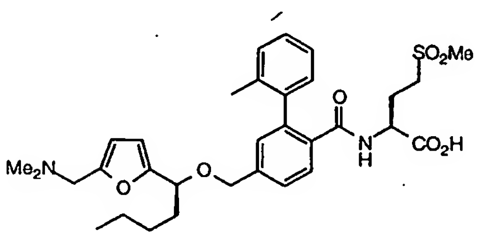
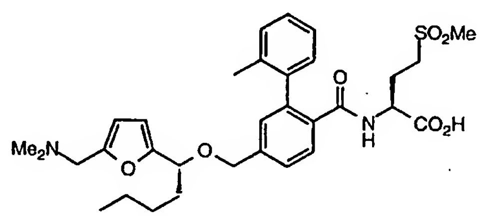

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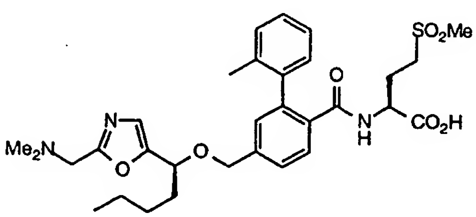
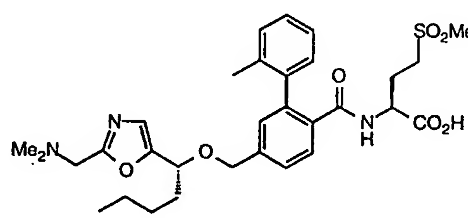

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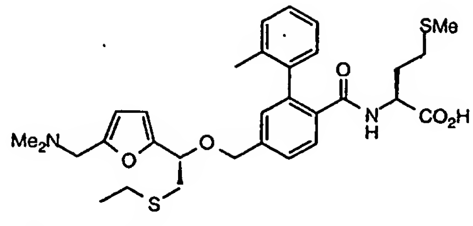
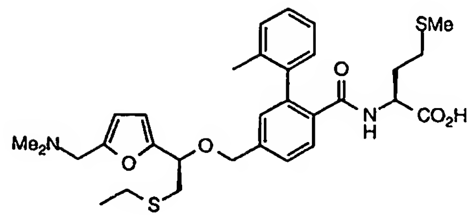

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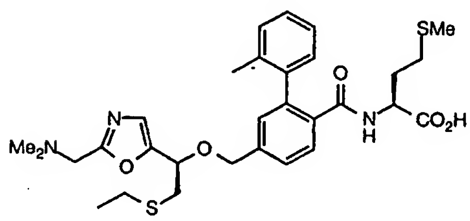
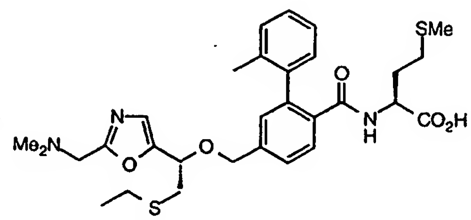

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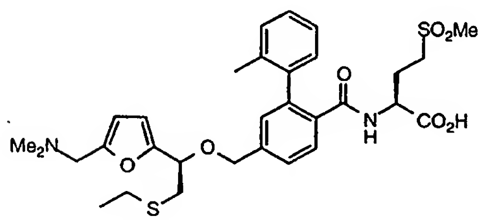
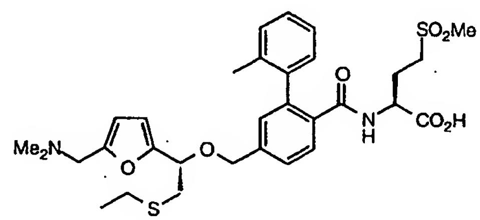

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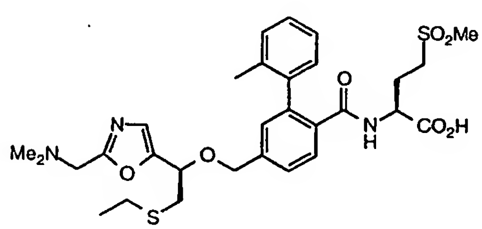
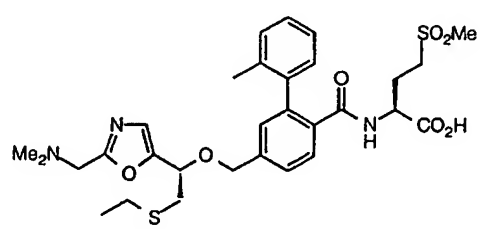

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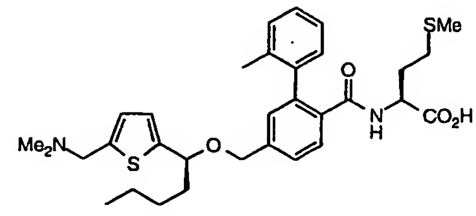
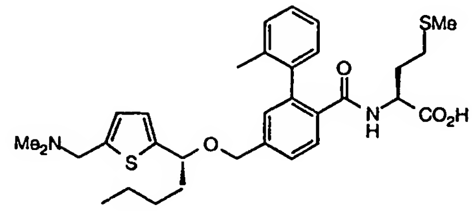

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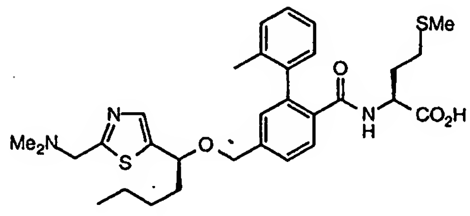
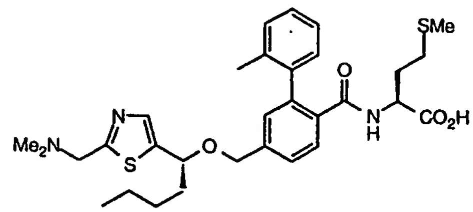

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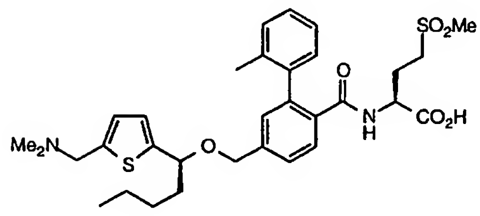
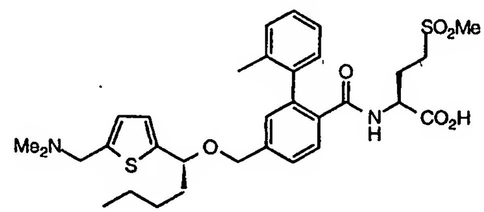

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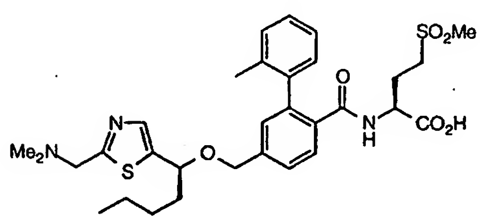
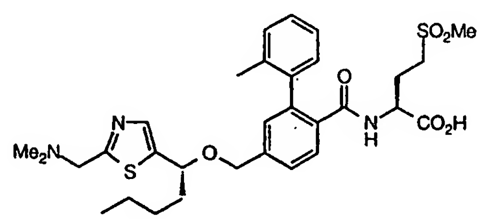

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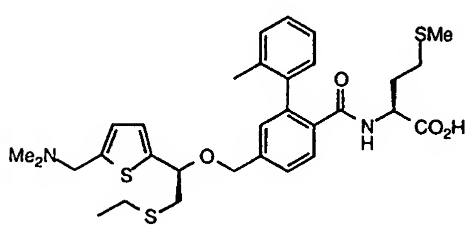
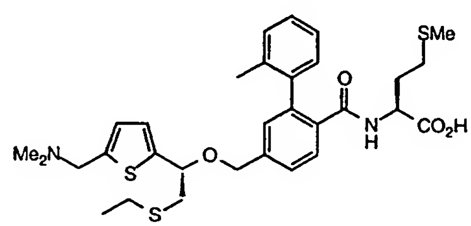

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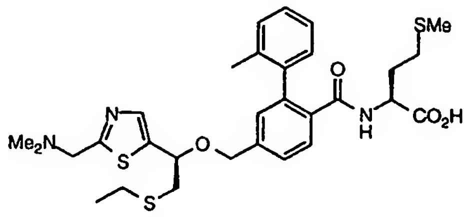

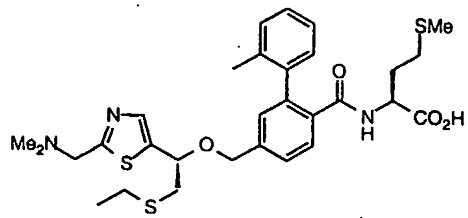

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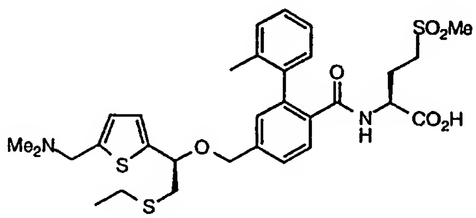

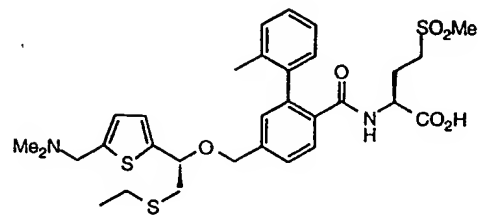

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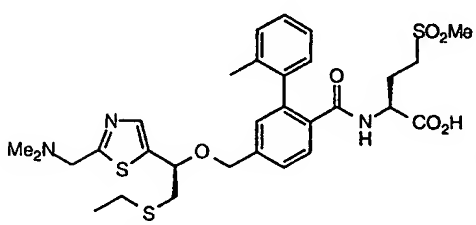

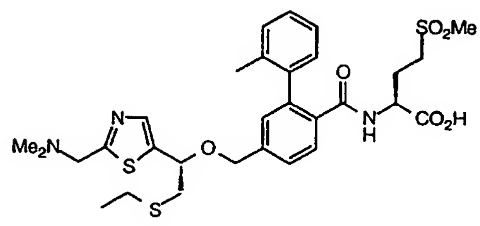

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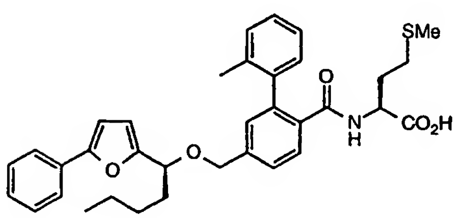

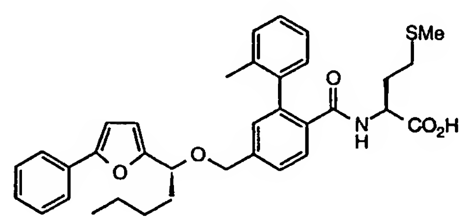

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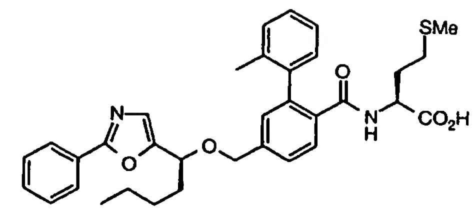 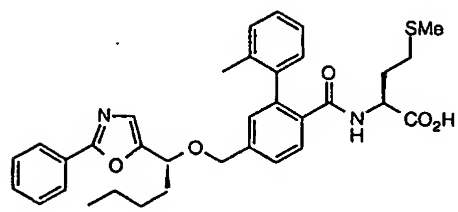

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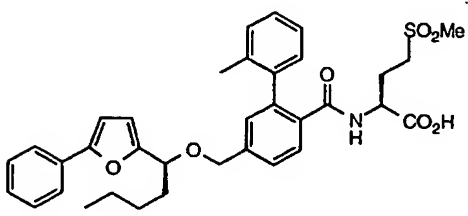 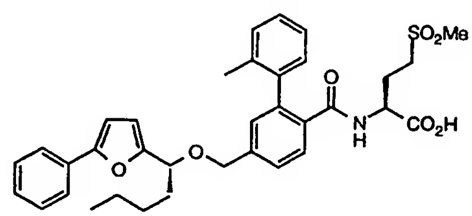

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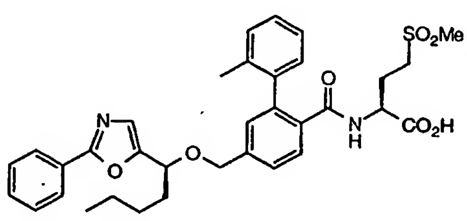 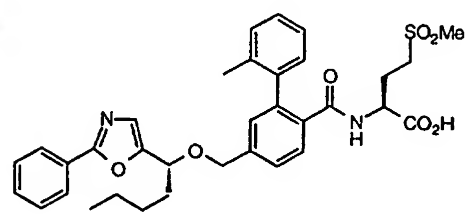

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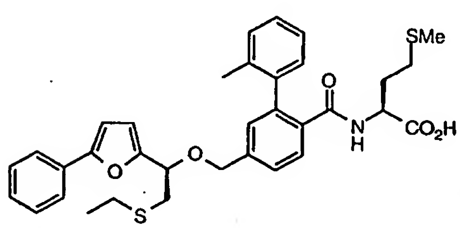 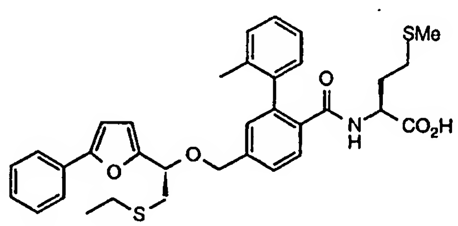

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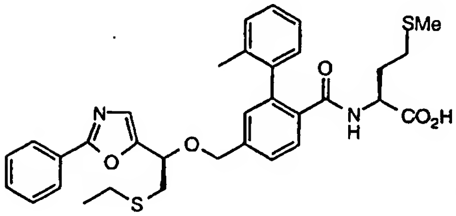 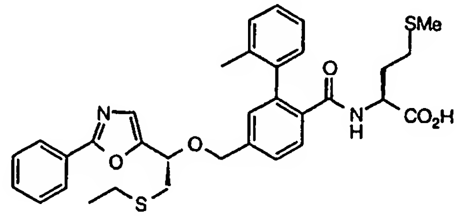

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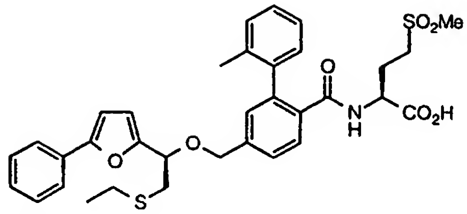
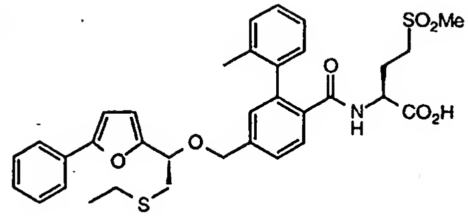

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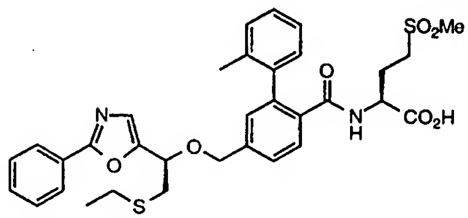
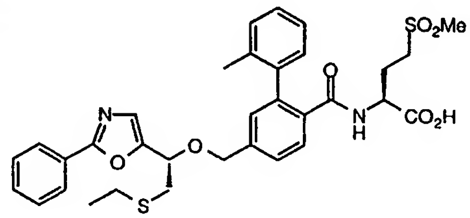

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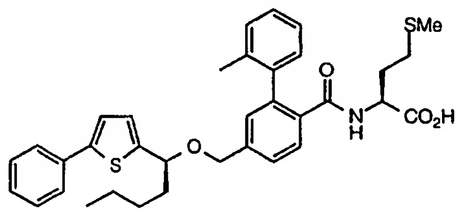
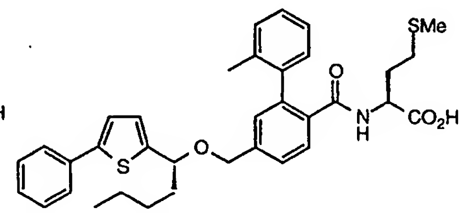

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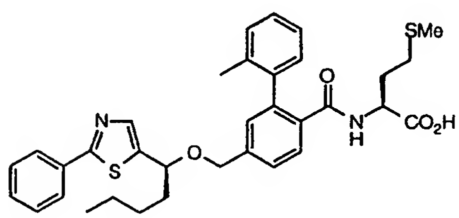
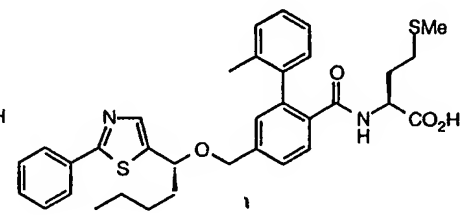

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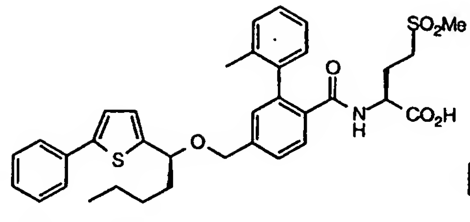
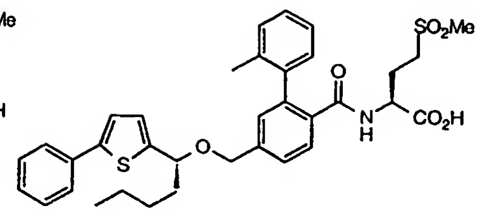

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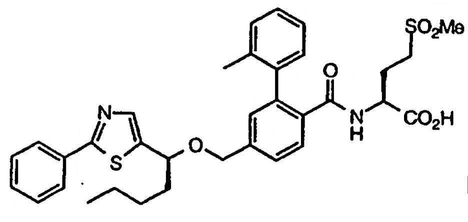
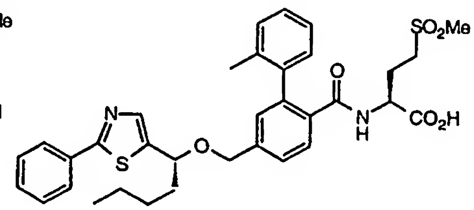

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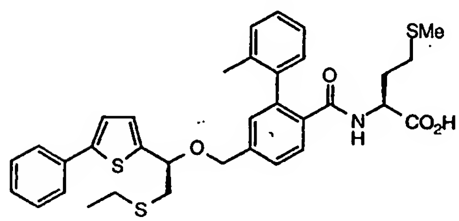
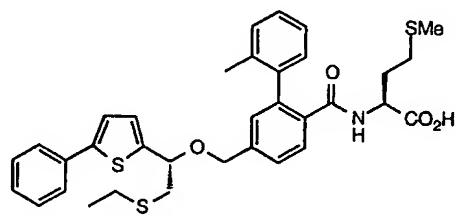

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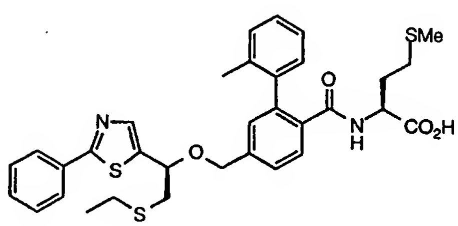
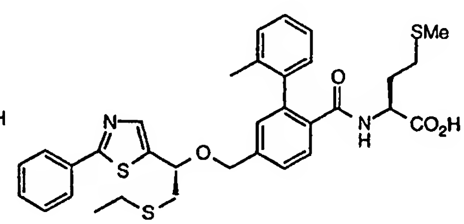

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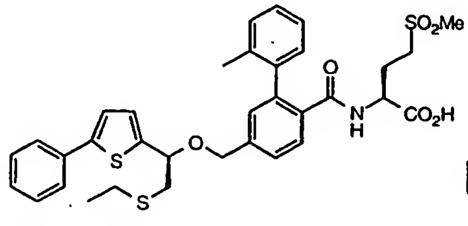
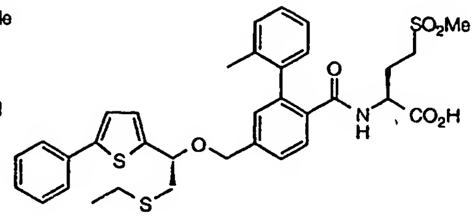

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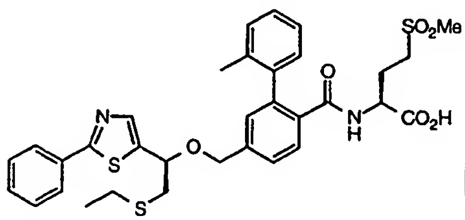
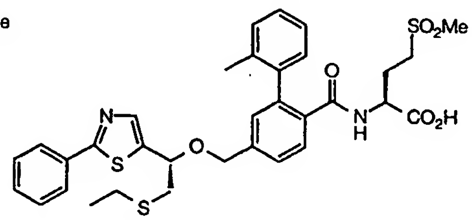

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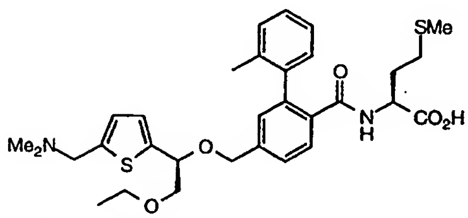
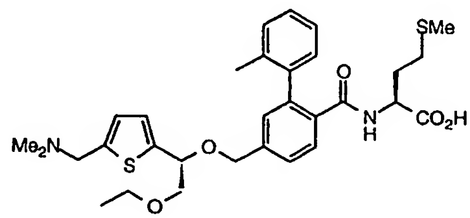

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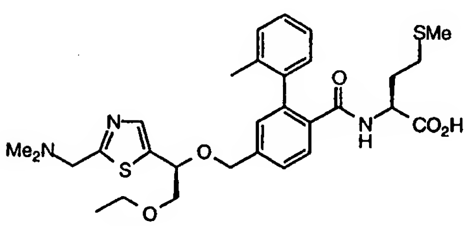
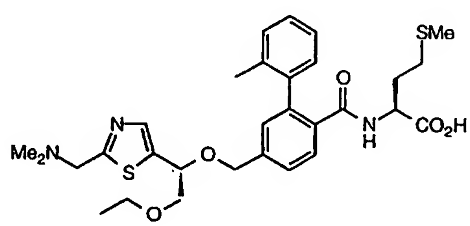

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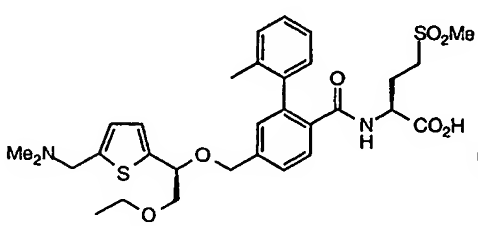
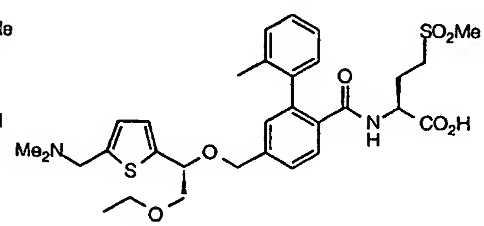

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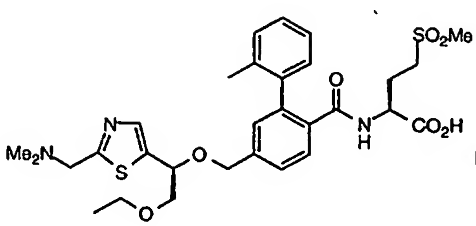

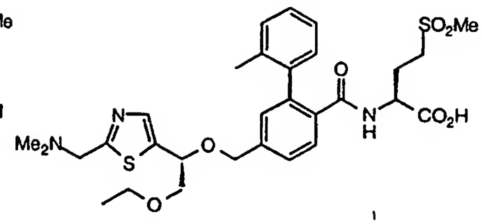

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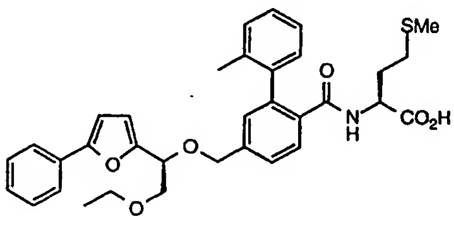

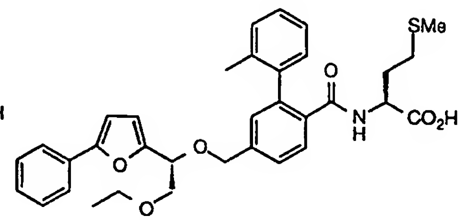

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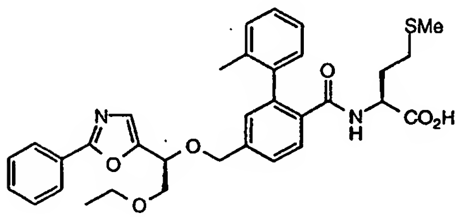

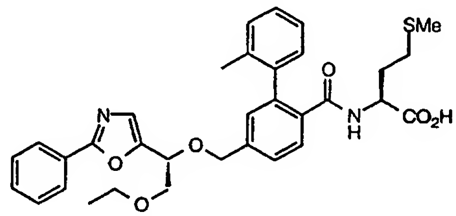

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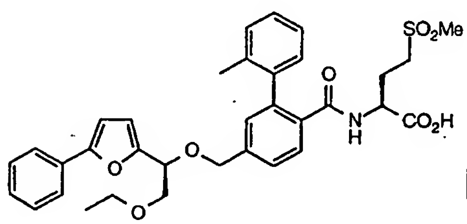

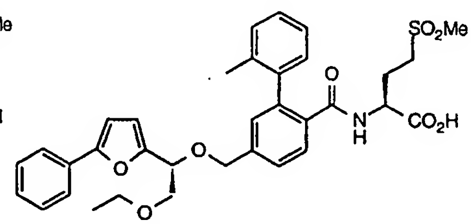

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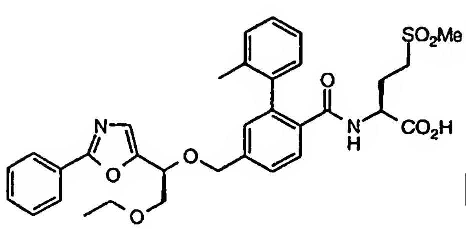

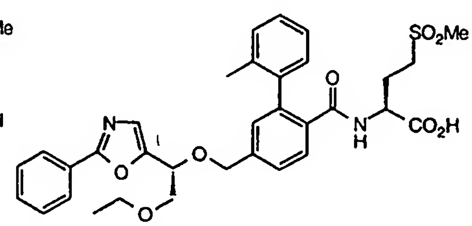

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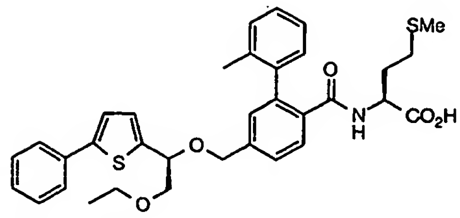 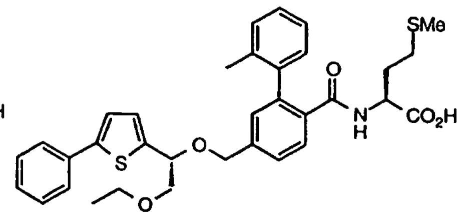

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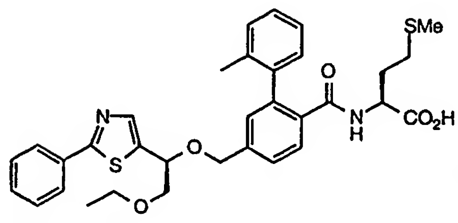 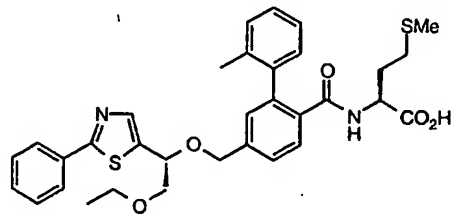

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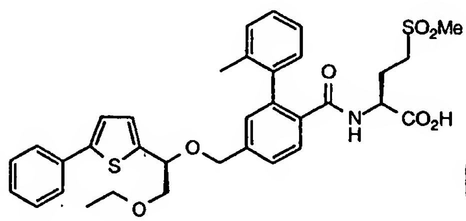 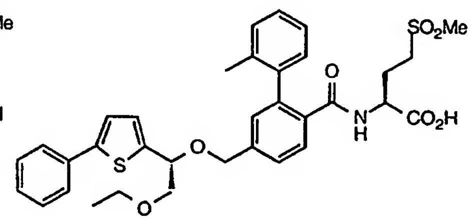

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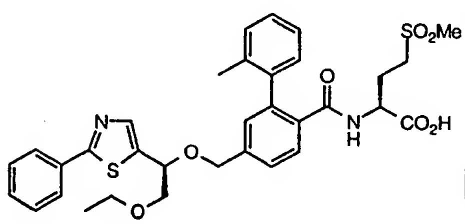 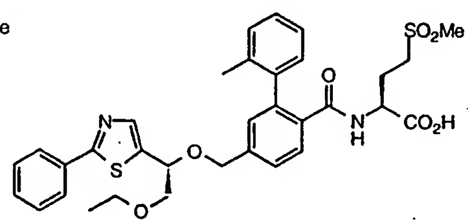

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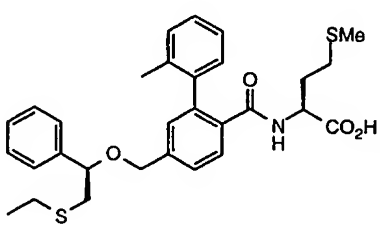 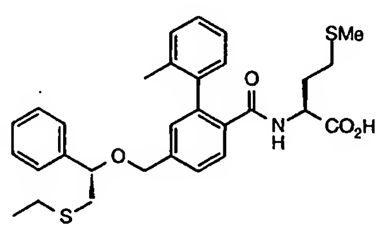

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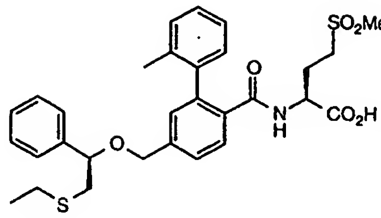
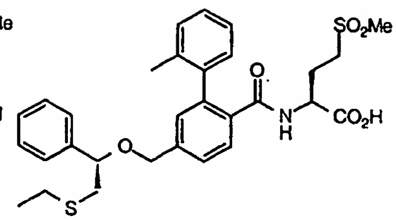

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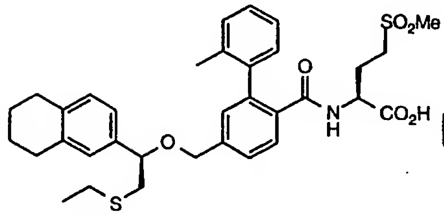
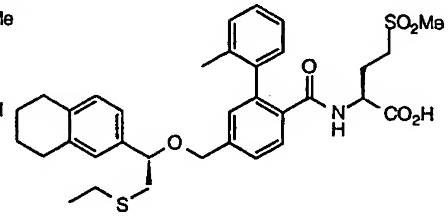

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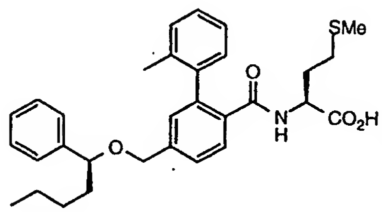
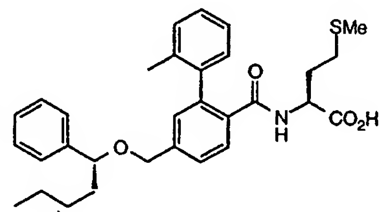

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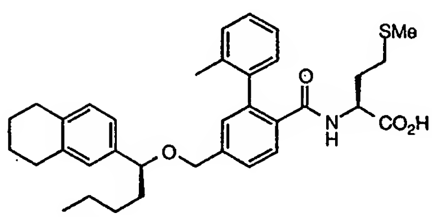
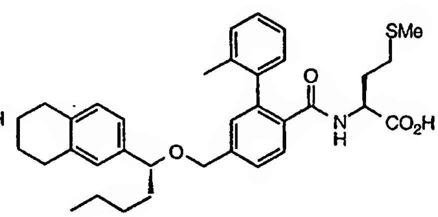

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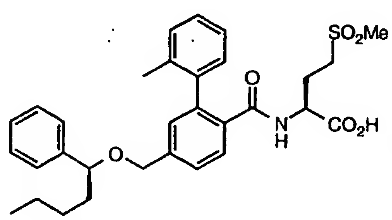
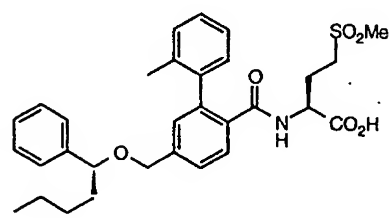

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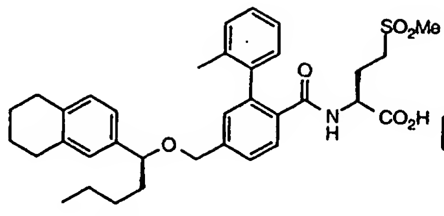
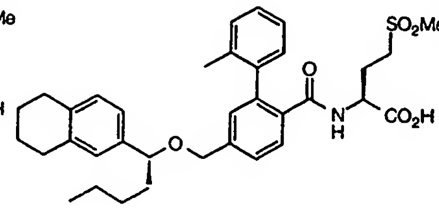

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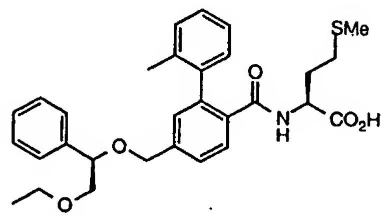
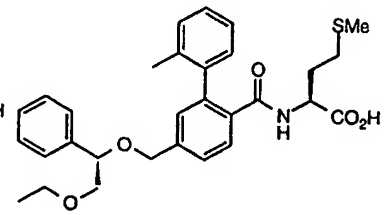

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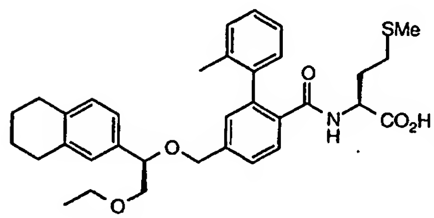
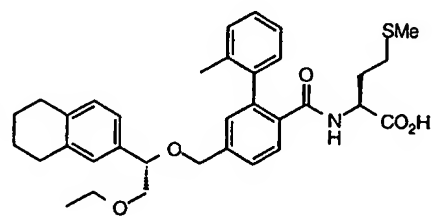

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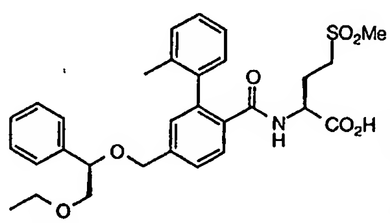
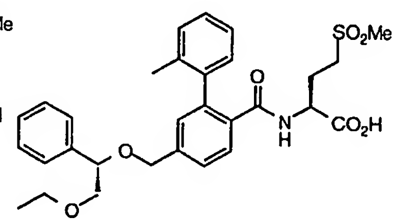

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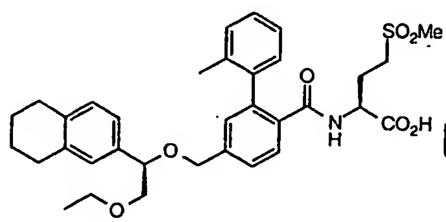
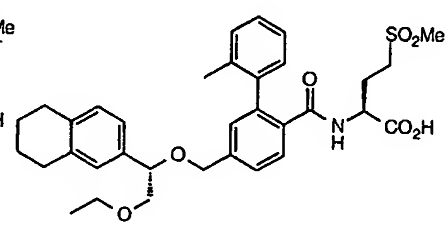

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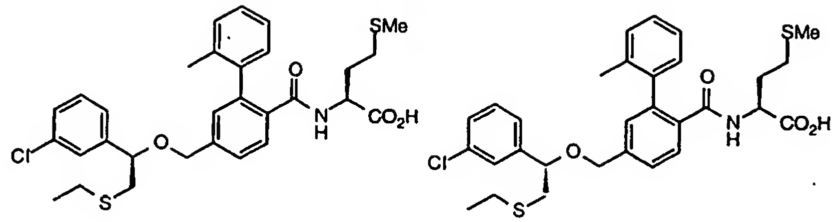

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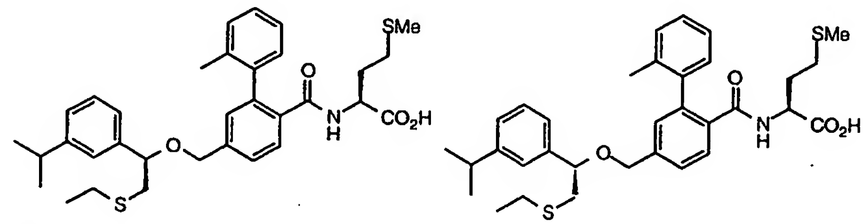

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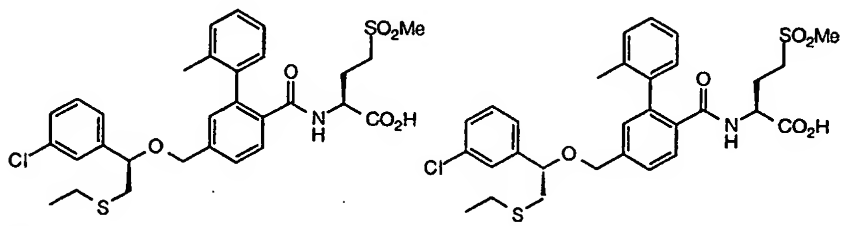

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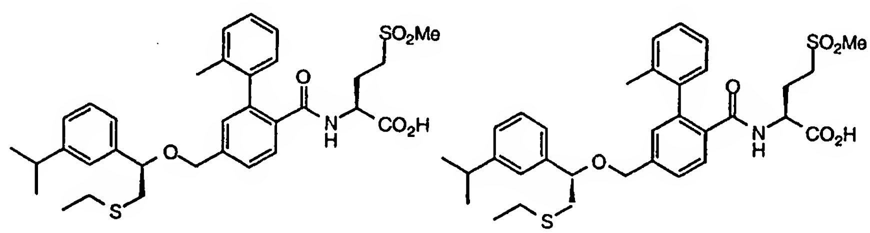

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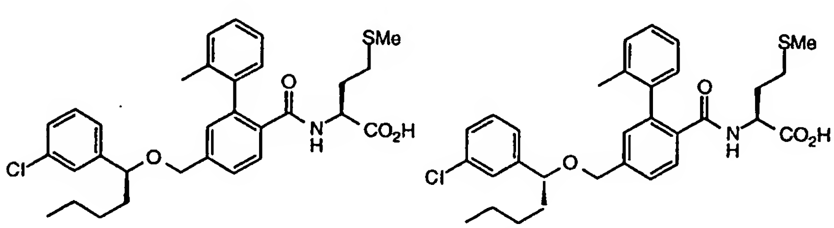

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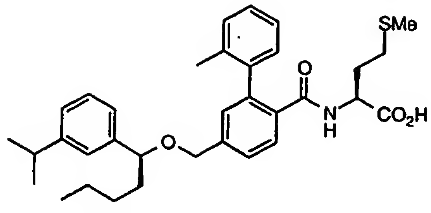
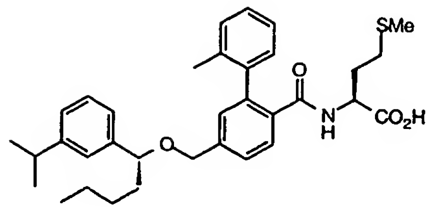

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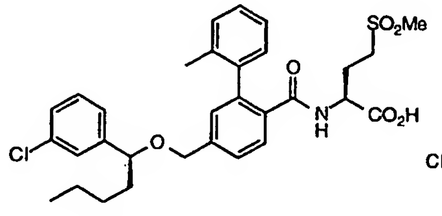
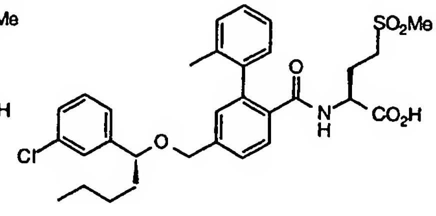

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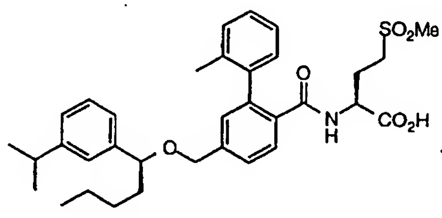
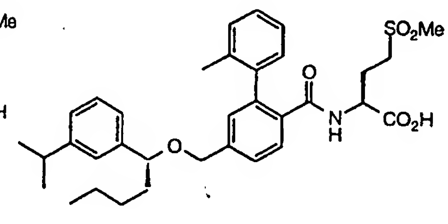

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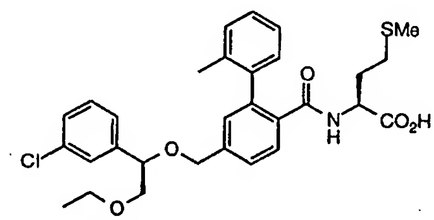
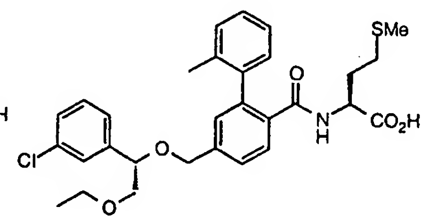

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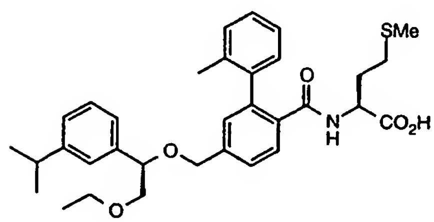
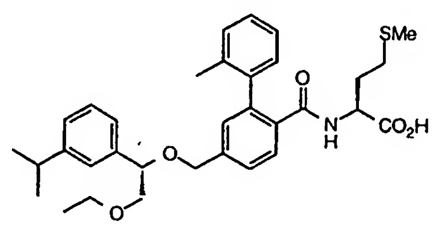

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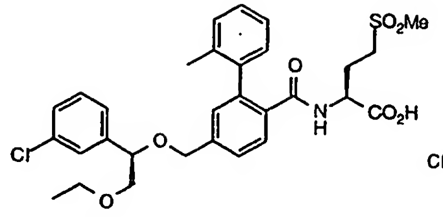
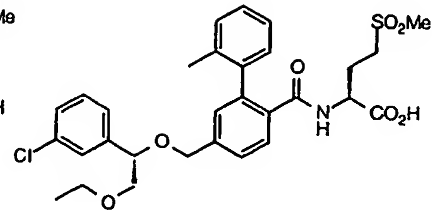

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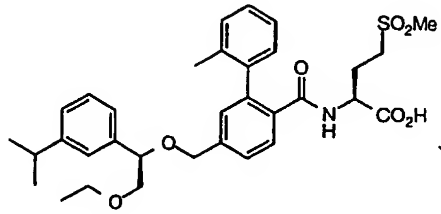
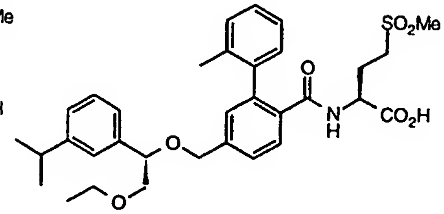

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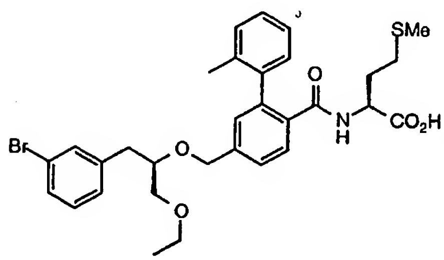
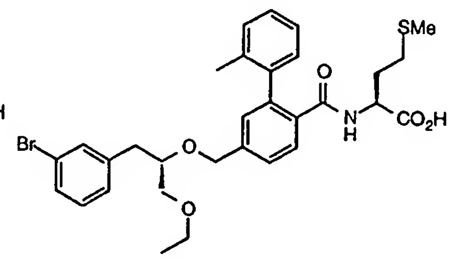

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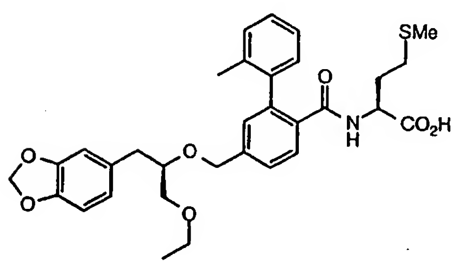
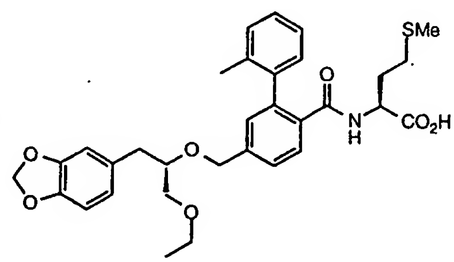

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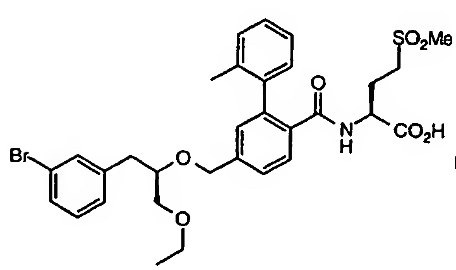
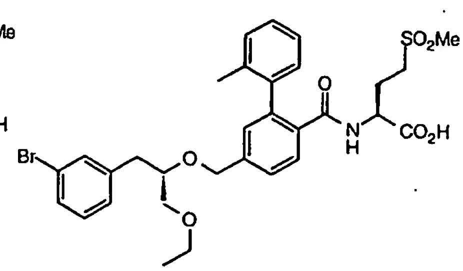

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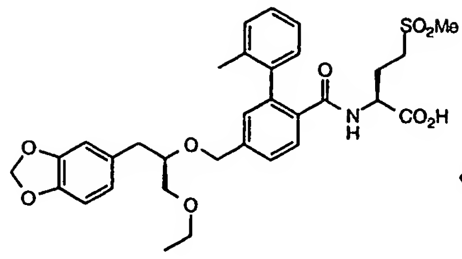
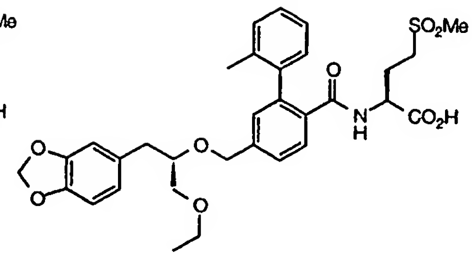

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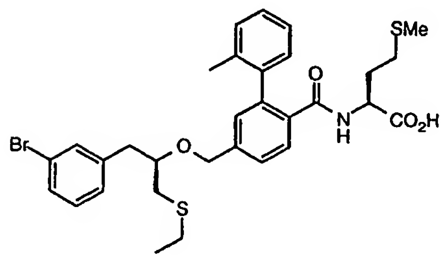
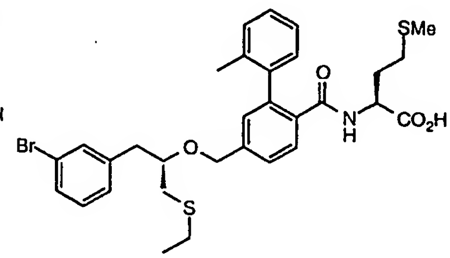

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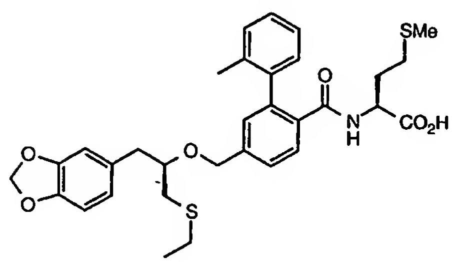
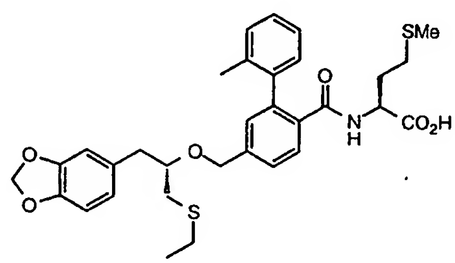

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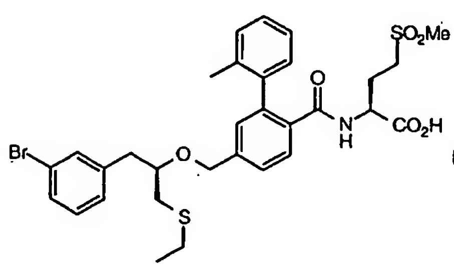
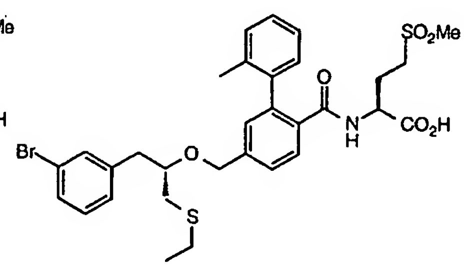

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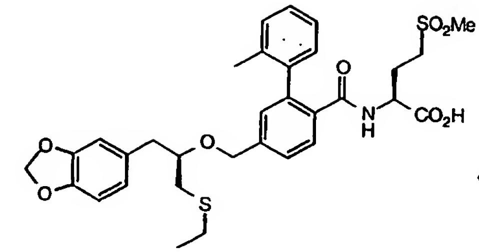
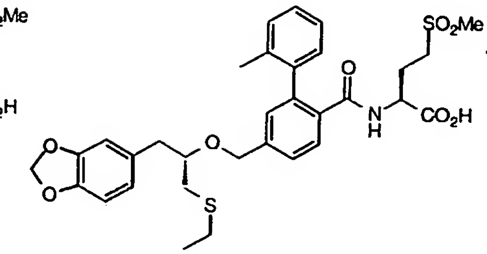

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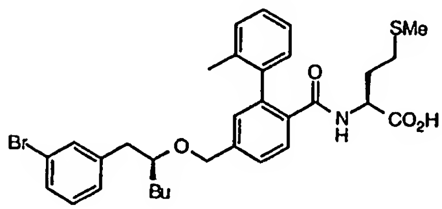
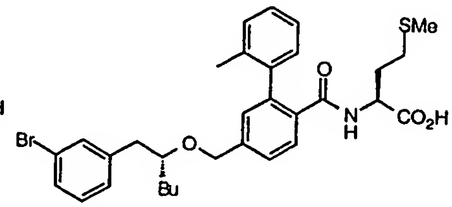

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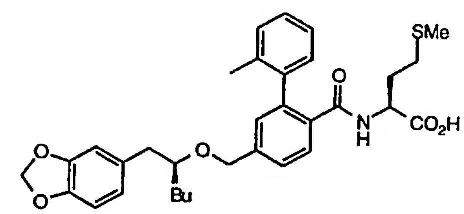
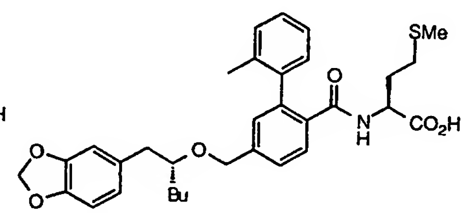

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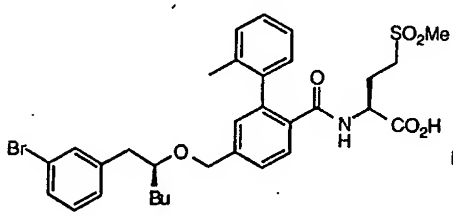
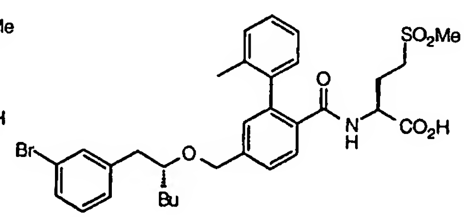

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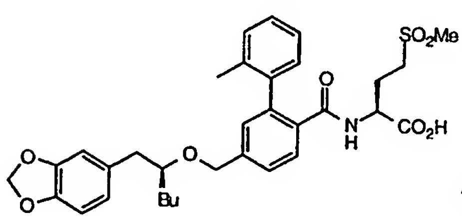
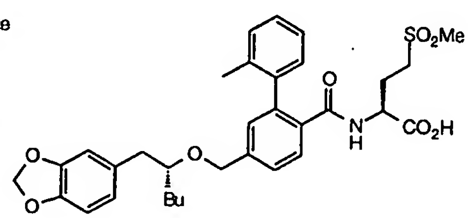

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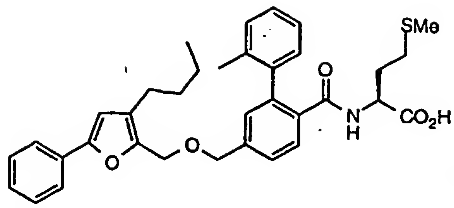

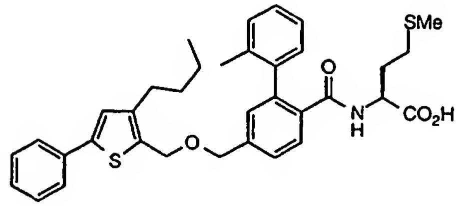

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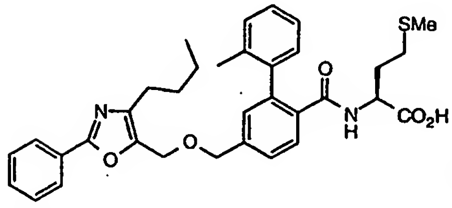

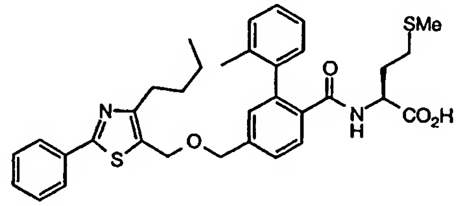

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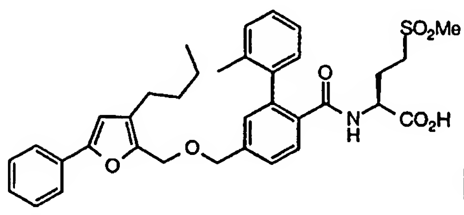

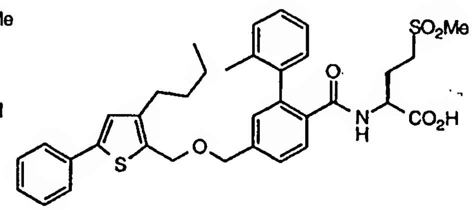

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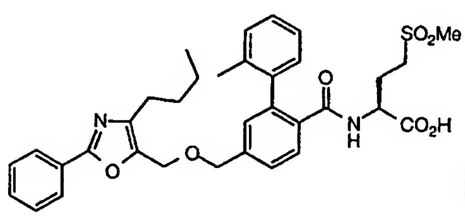

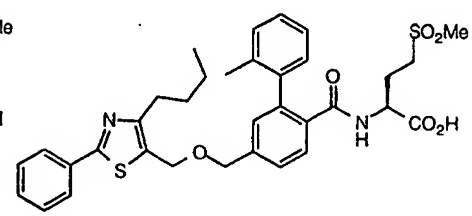

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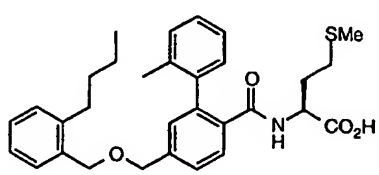

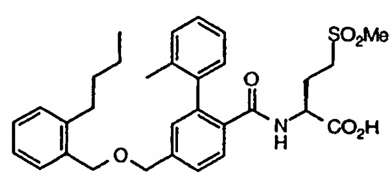

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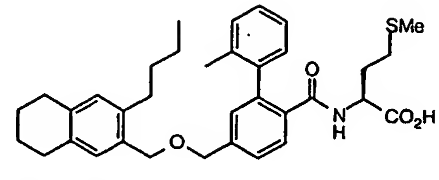
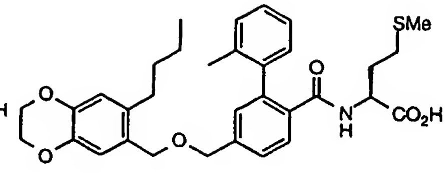

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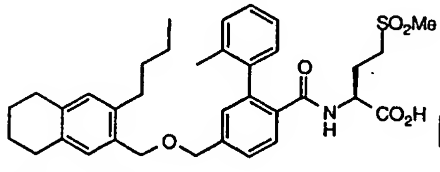
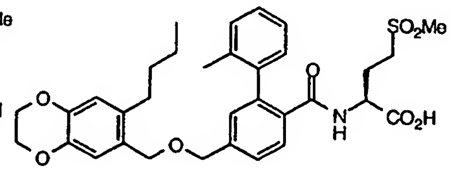

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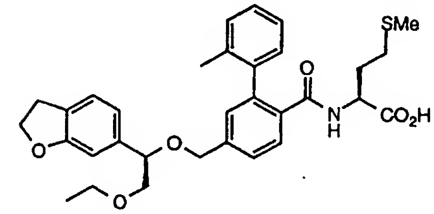
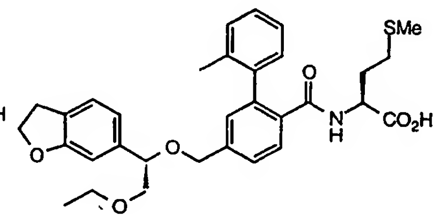

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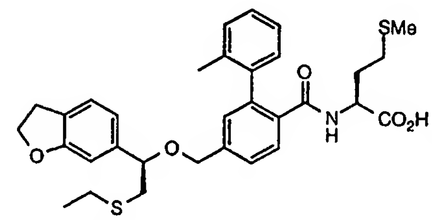
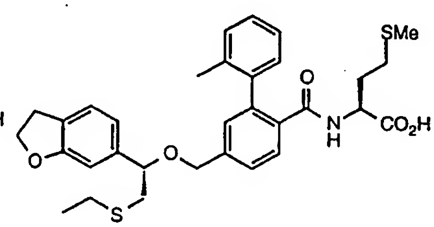

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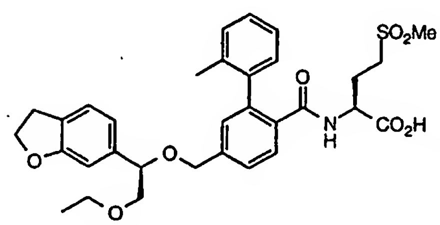
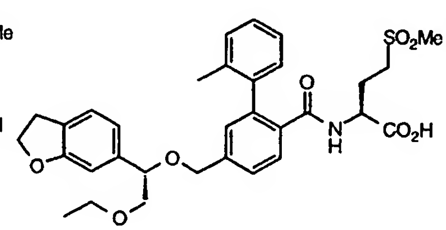

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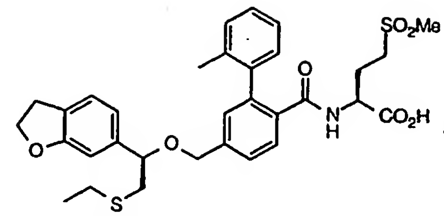
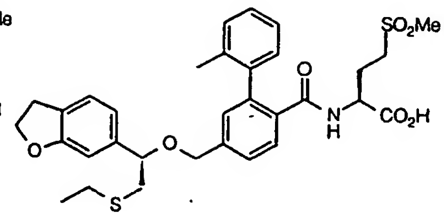

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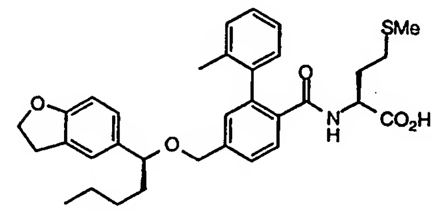
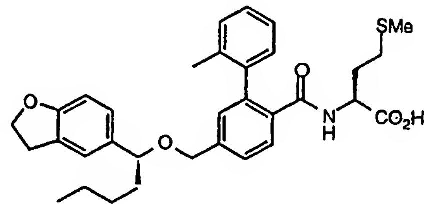

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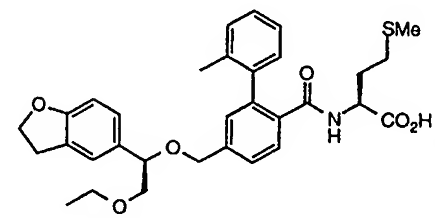
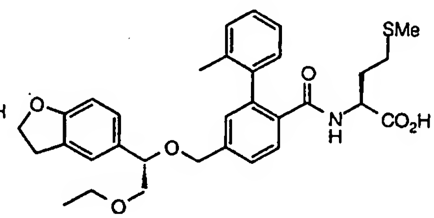

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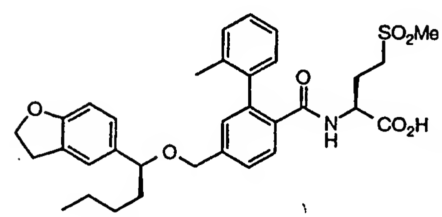
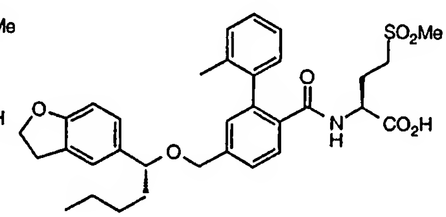

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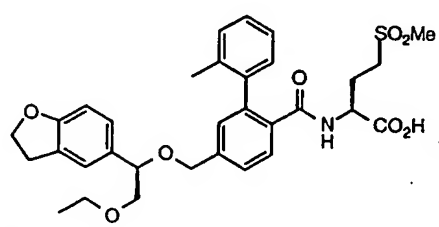
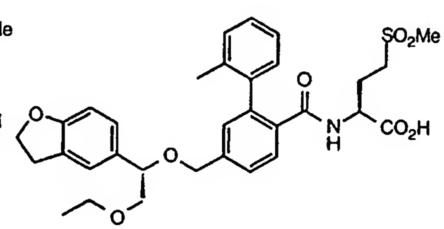

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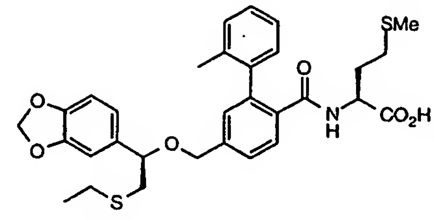
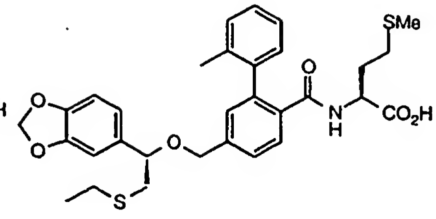

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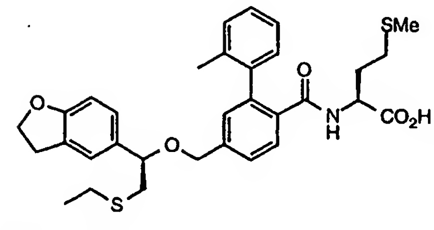
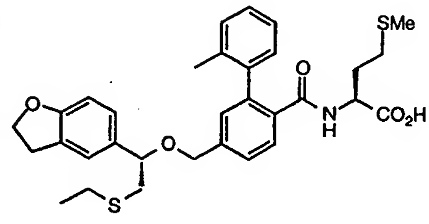

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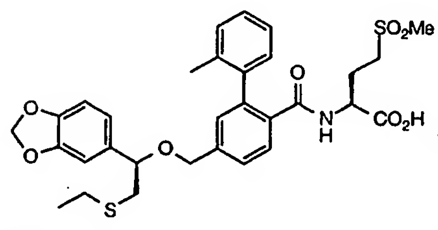
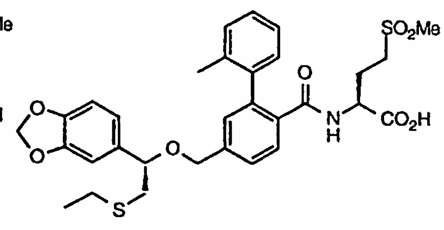

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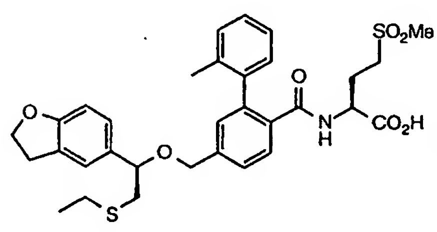
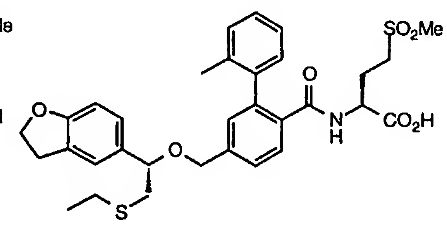

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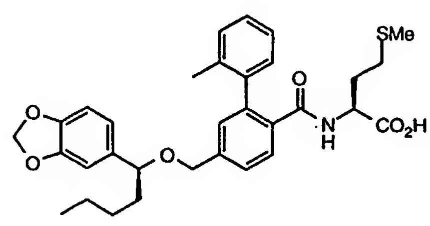
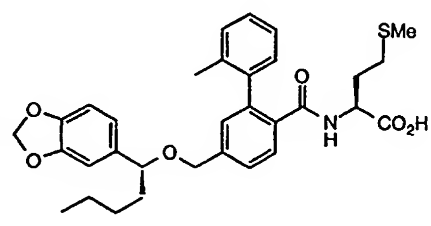

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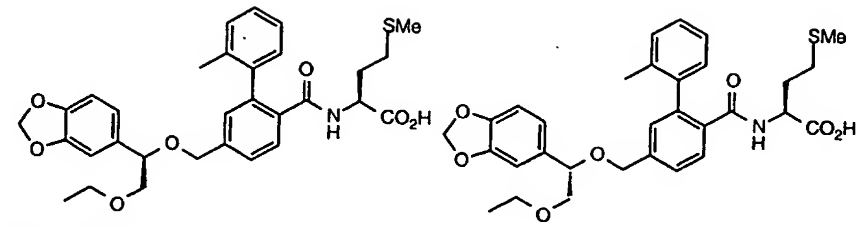

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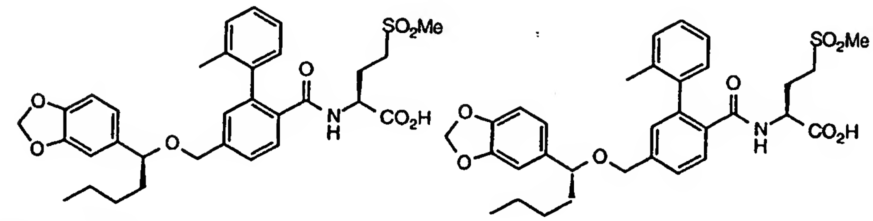

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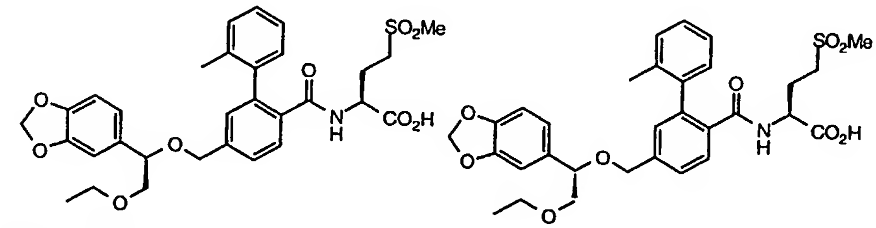

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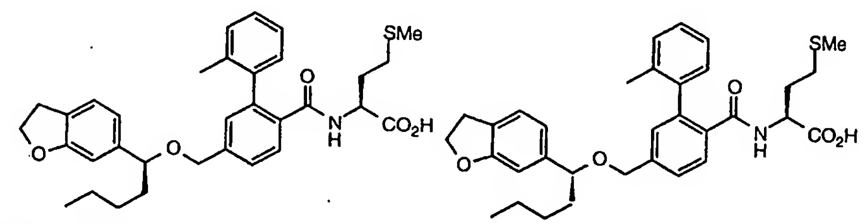

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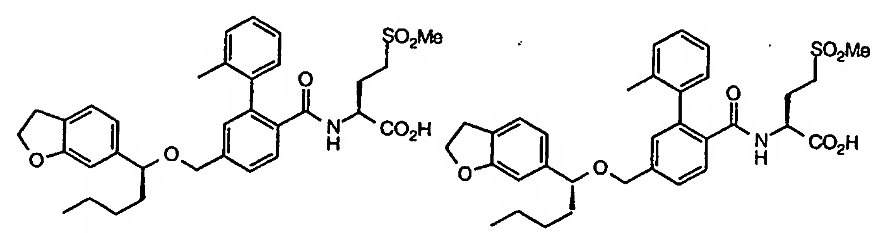

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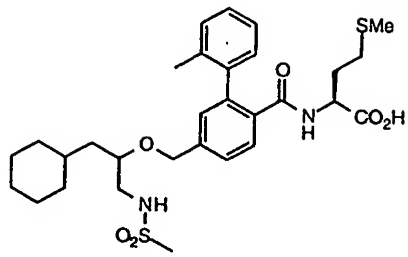
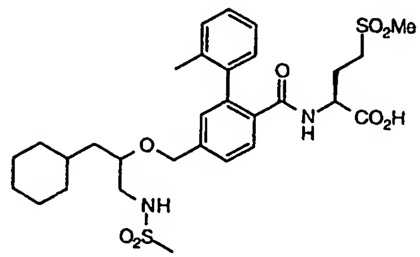

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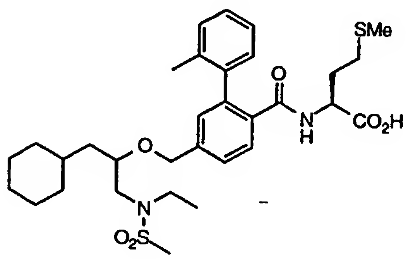
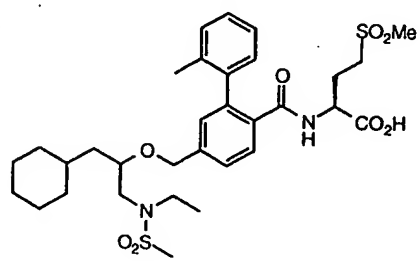

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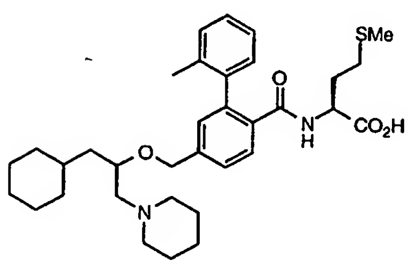
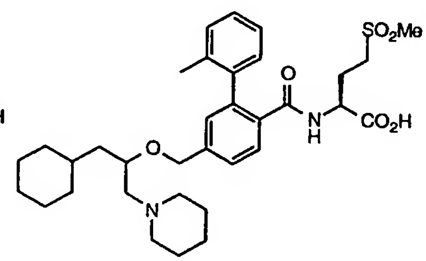

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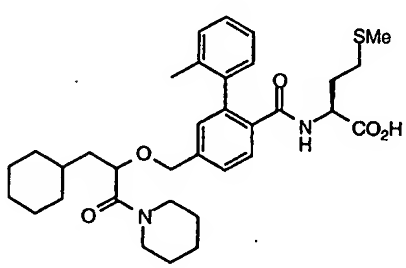
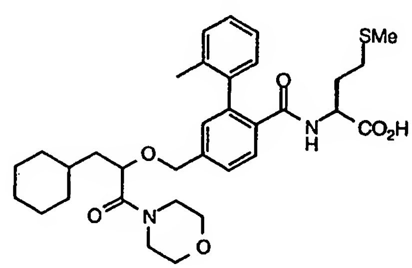

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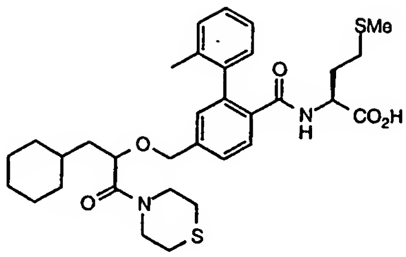
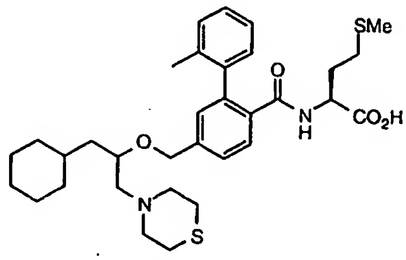

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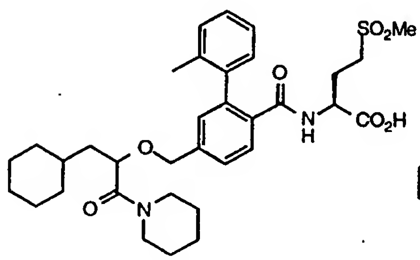
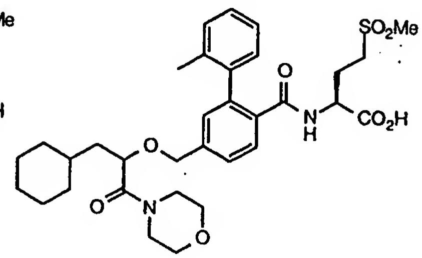

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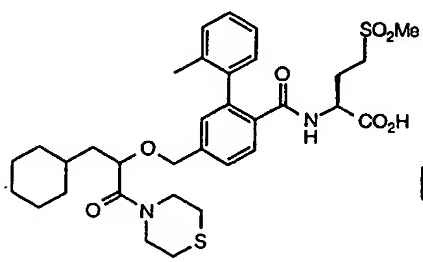
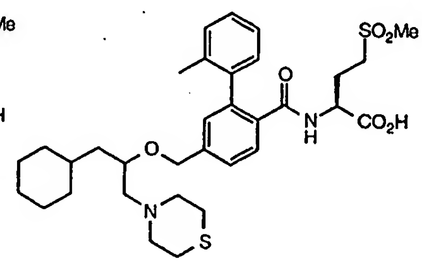

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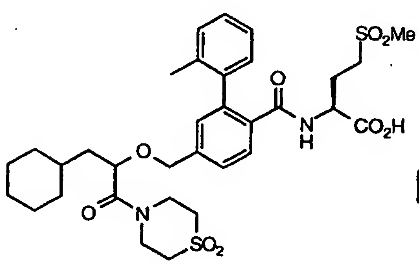
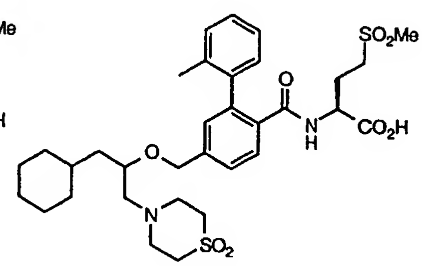

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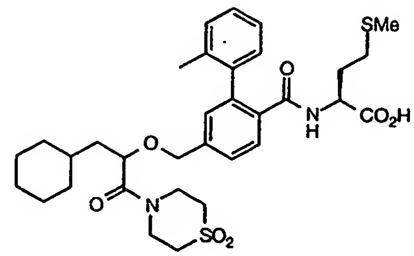

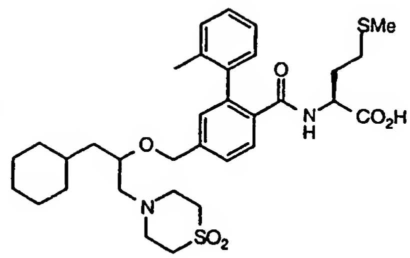

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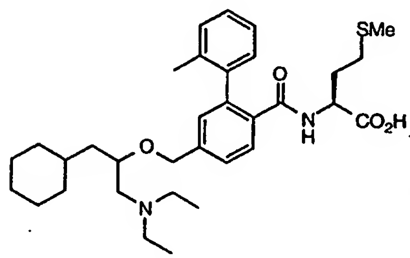

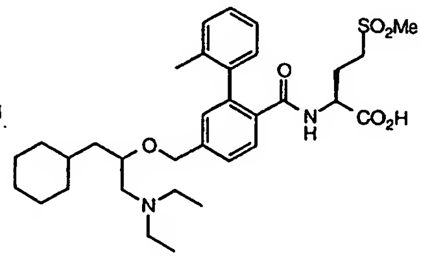

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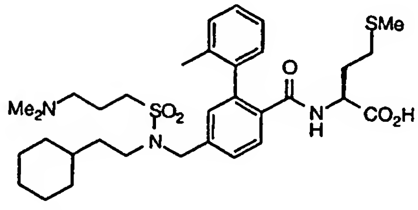
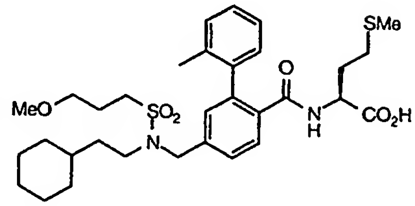
Table 8. Sulfonamides of the Type $ASO_2(B)N\text{-}L_1$

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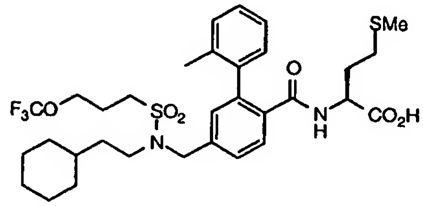
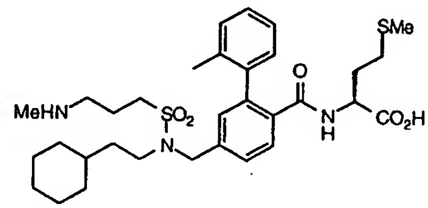

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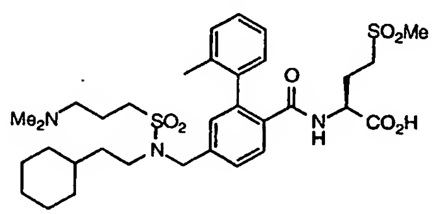
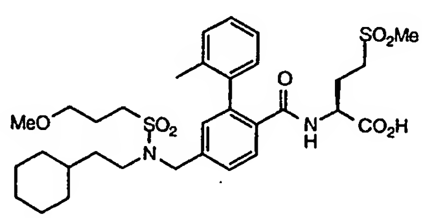

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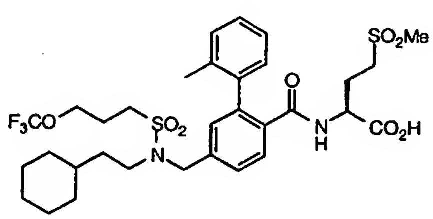
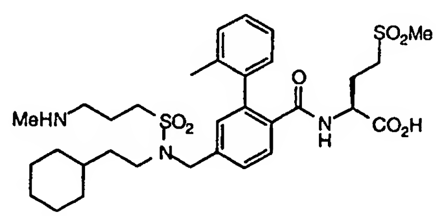

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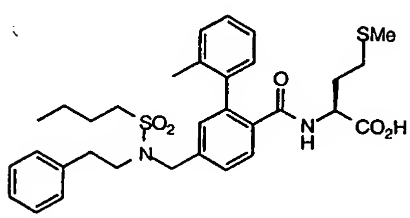
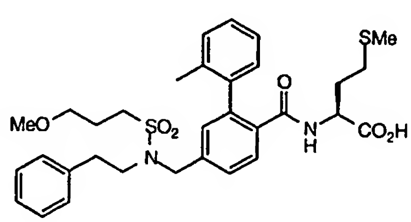

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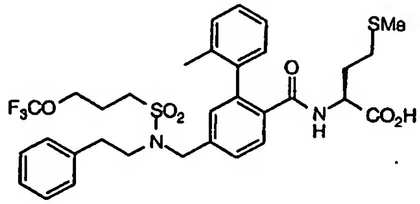
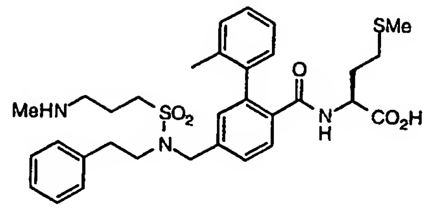

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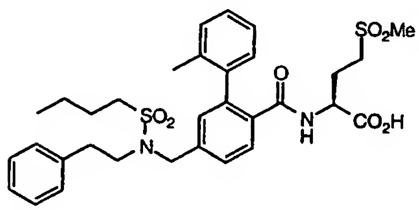
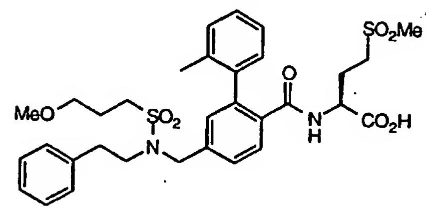

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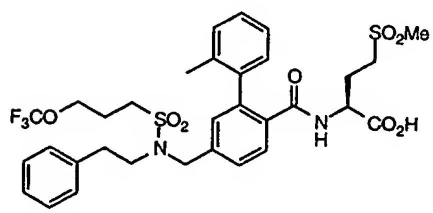
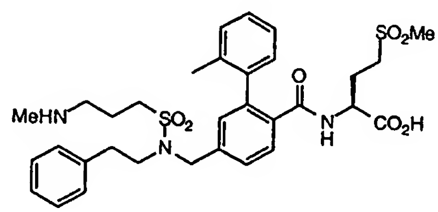

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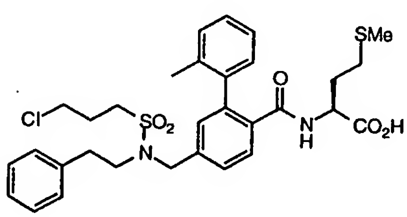
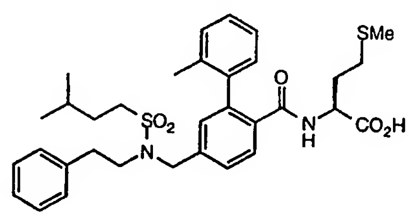

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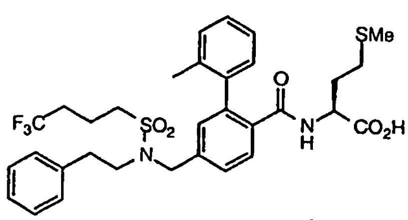
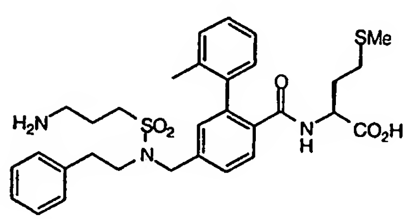

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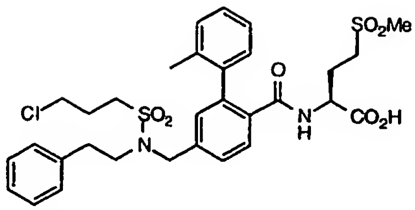
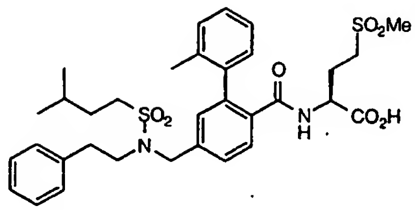

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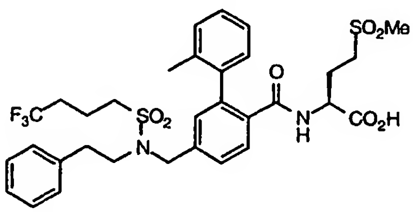
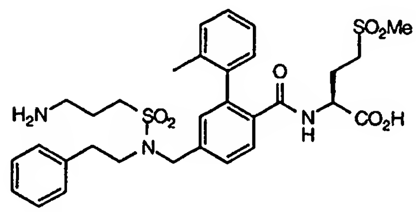

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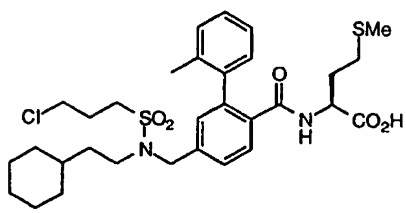
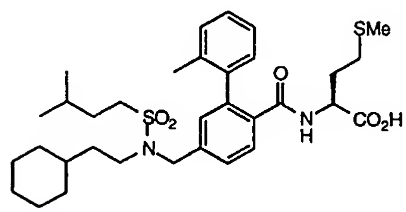

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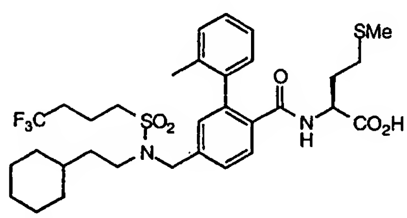
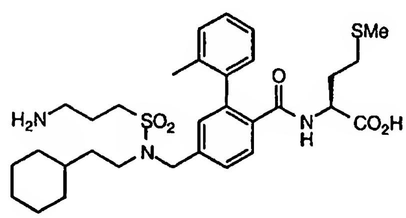

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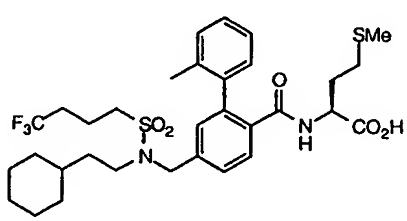
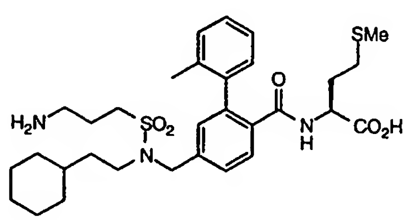

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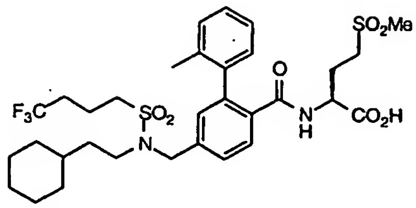
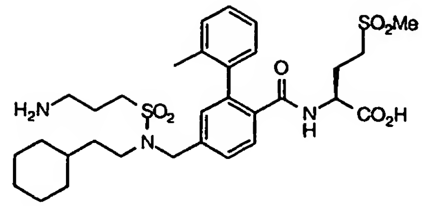
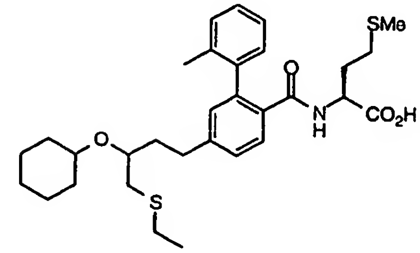
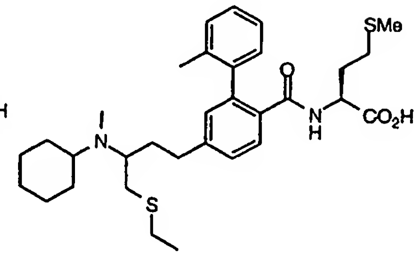




31 **32**

Table 9. Hydrocarbons of the Type A(B)CH_2-L_1

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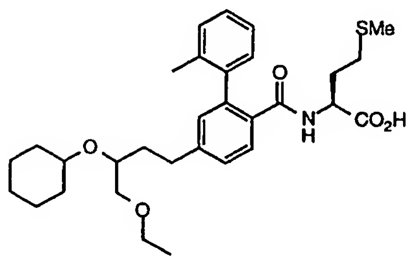
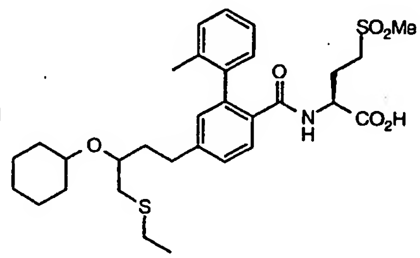

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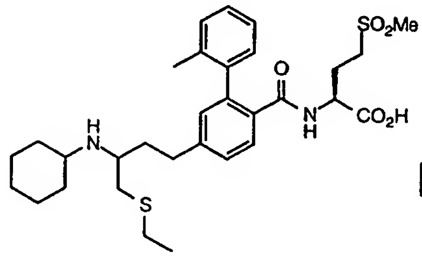
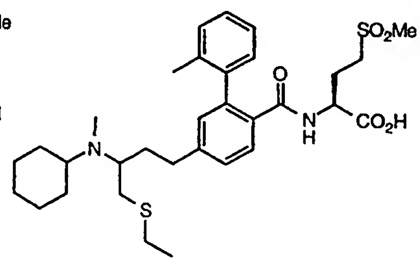

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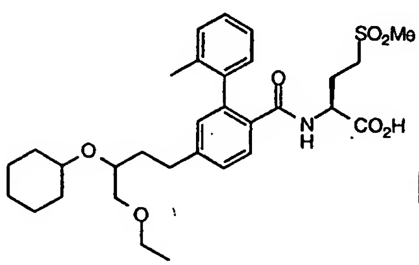
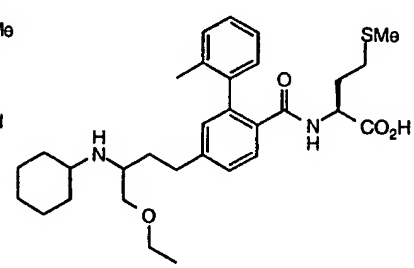

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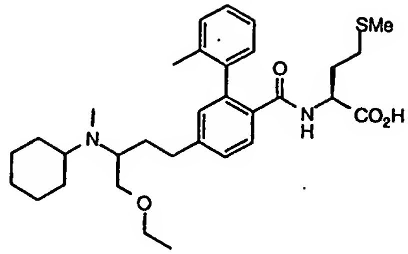
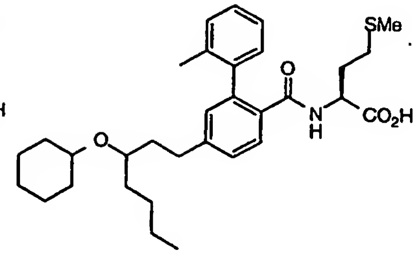

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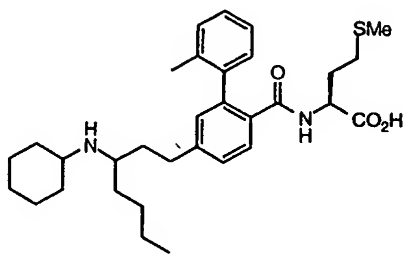
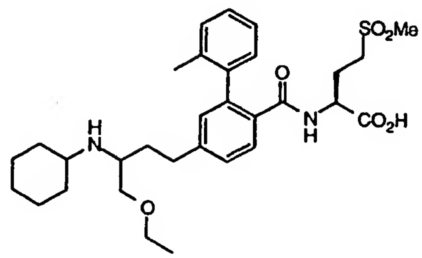

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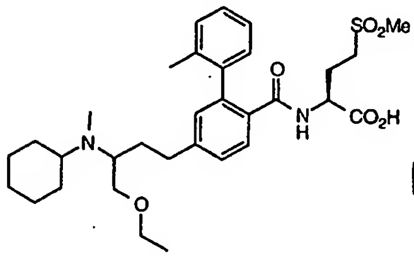
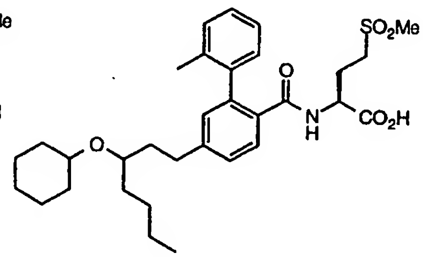

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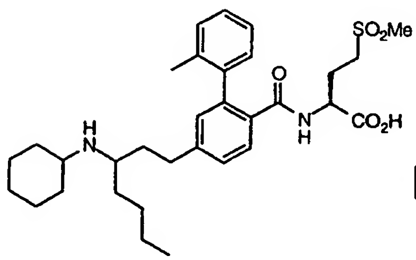
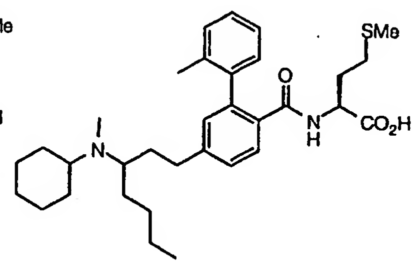

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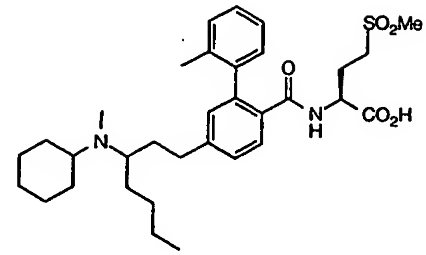

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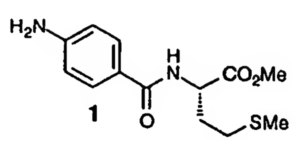
Table 10. Amines of the type B-NH_2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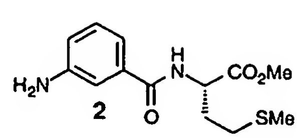
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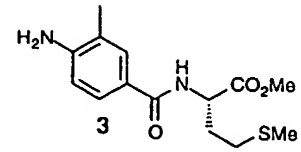
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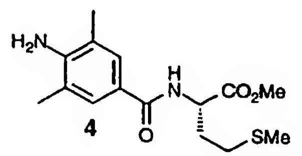
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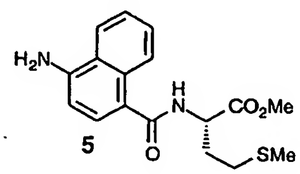
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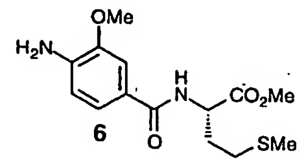
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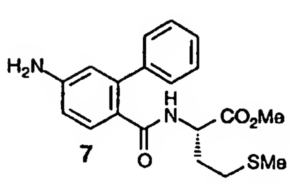
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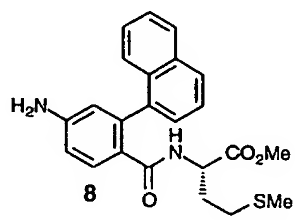
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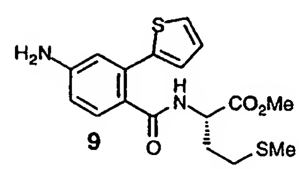
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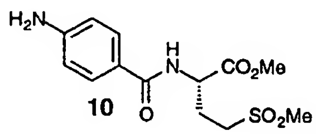
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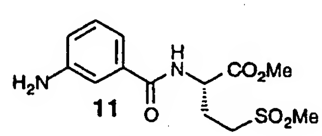
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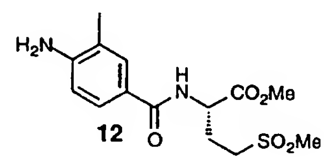
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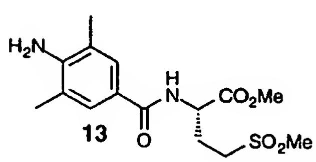
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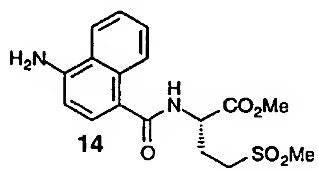
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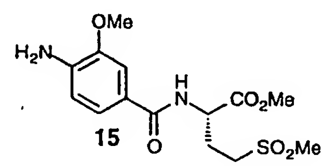
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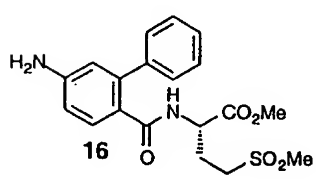
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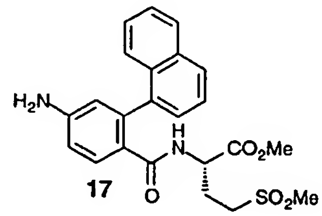
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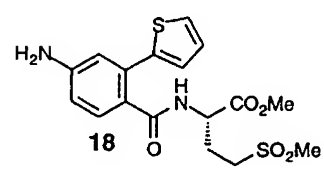
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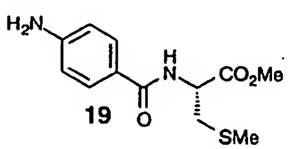
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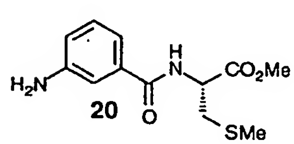
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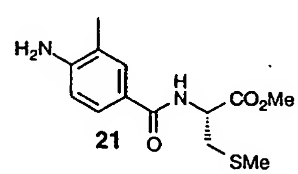
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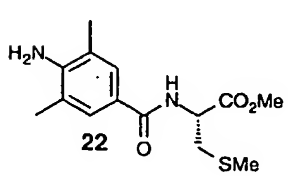
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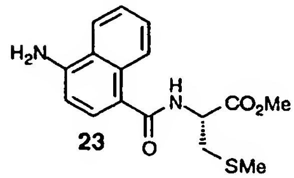
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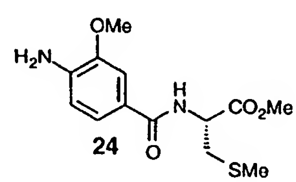
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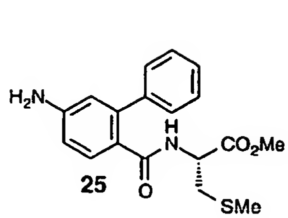
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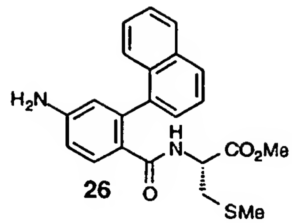
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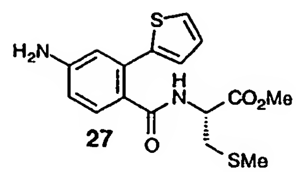
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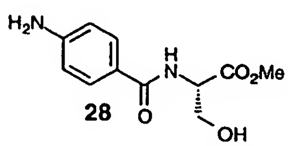
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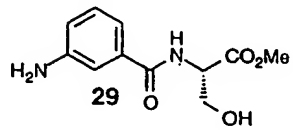
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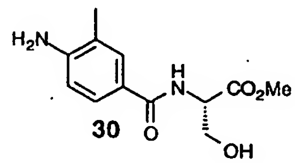
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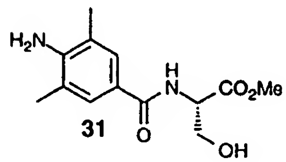
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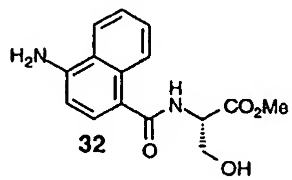
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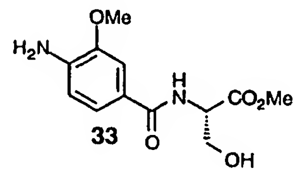
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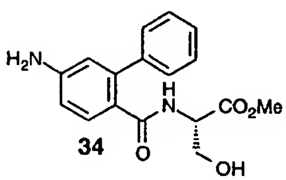
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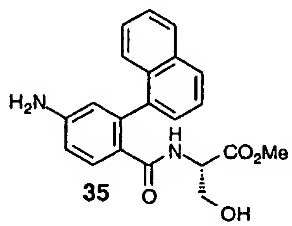
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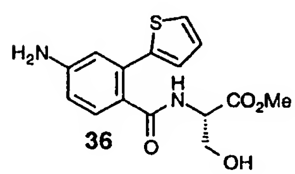
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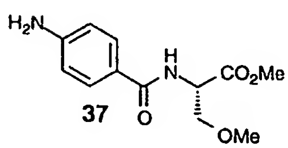
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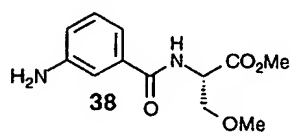
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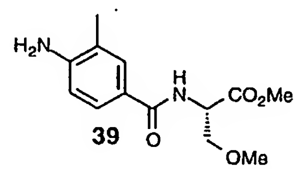
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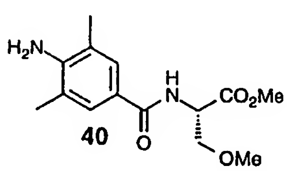
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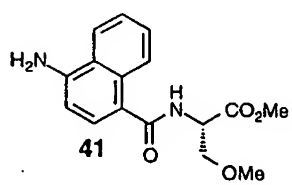
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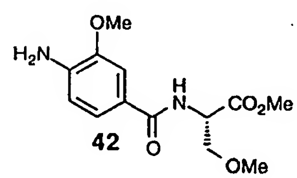
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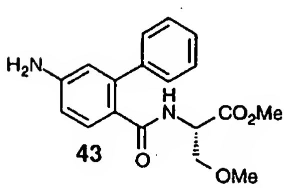
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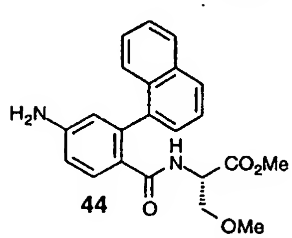
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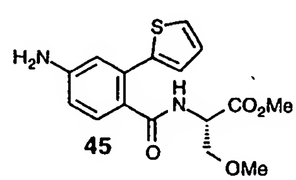
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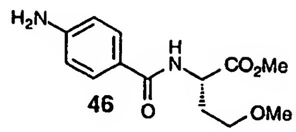
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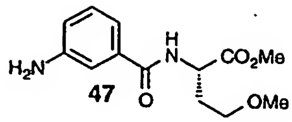
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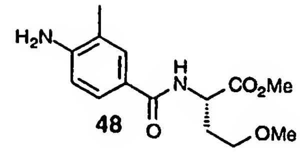
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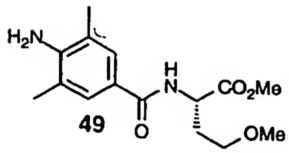
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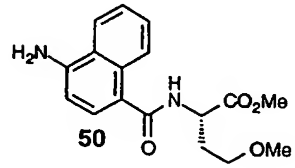
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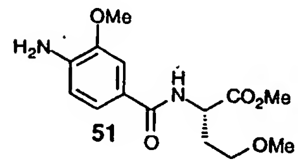
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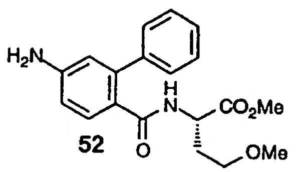
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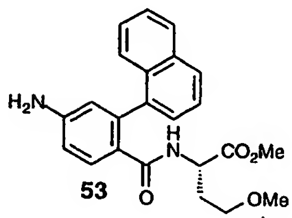
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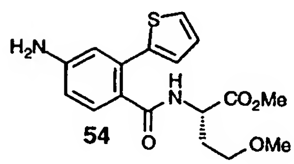
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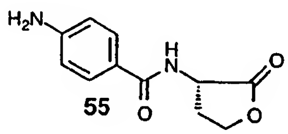
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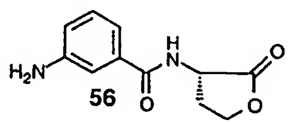
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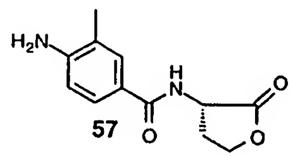
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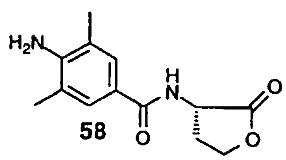
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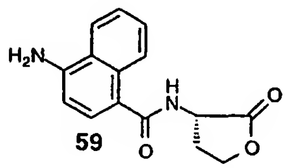
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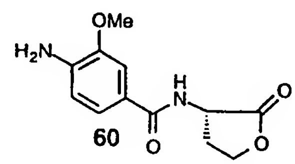
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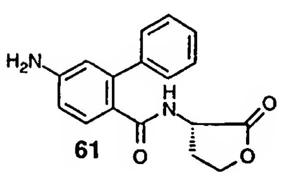
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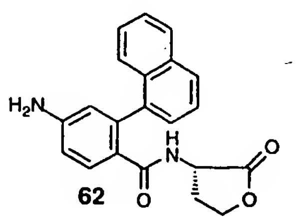
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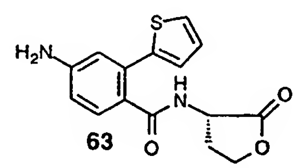
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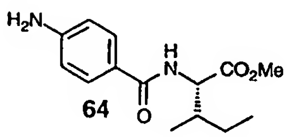
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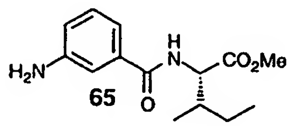
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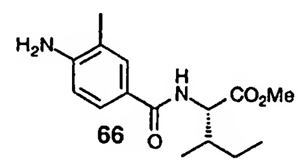
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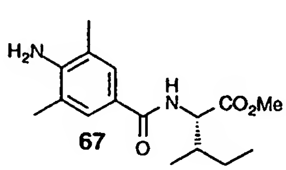
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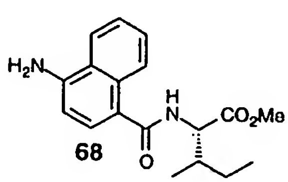
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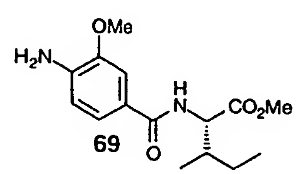
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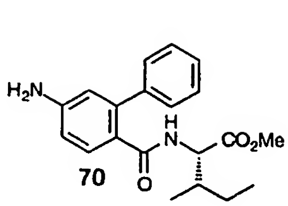
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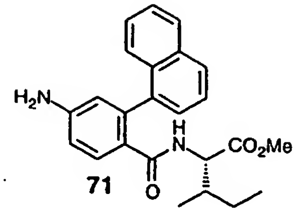
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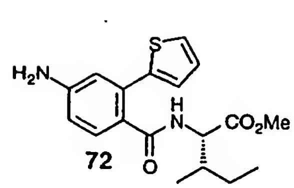
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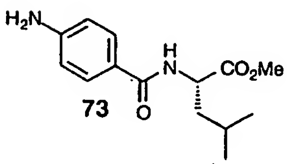
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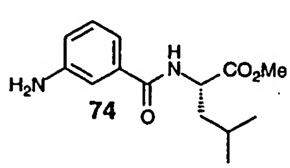
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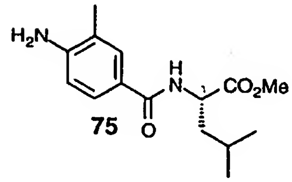
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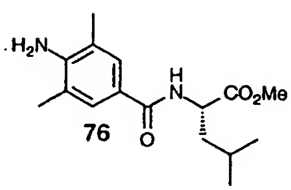
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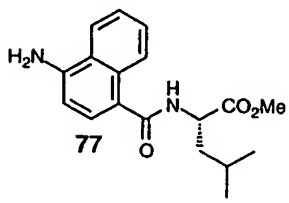
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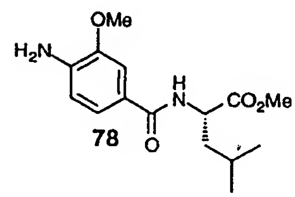
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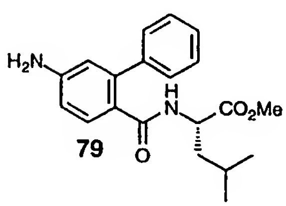
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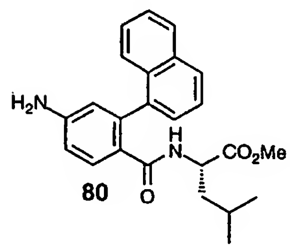
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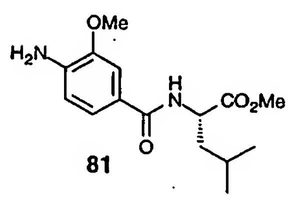
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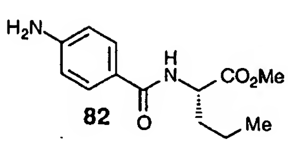
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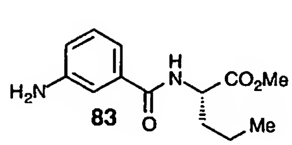
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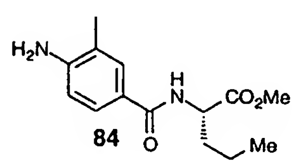
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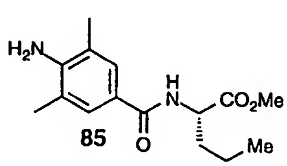
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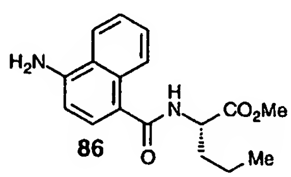
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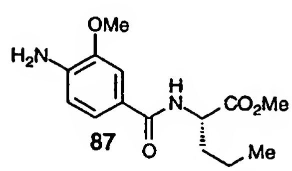
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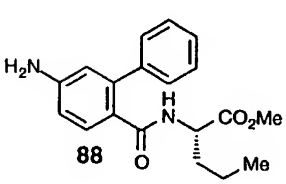
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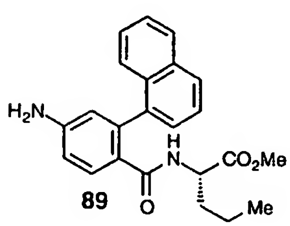
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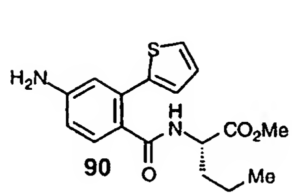
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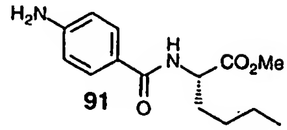
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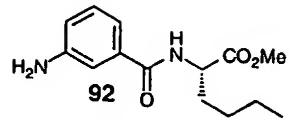
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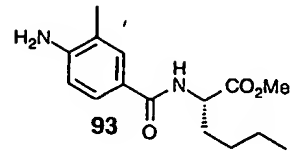
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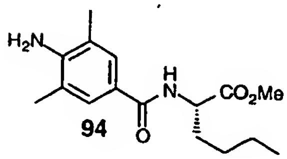
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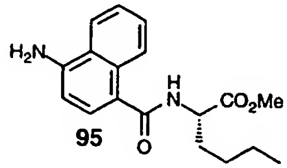
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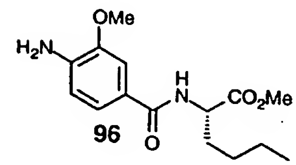
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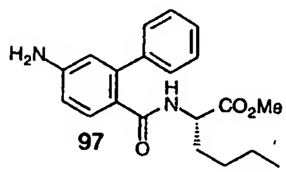
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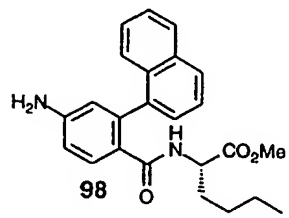
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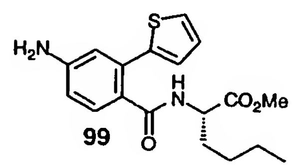
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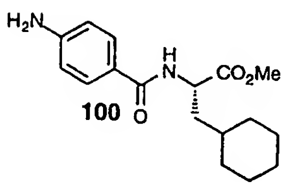
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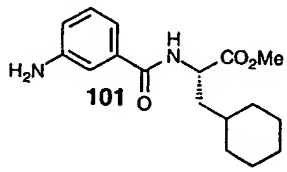
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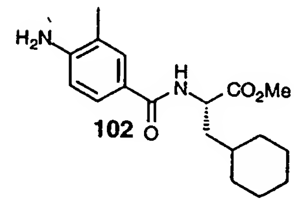
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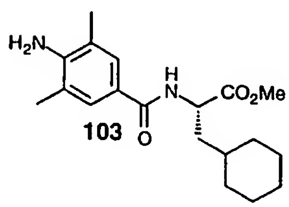
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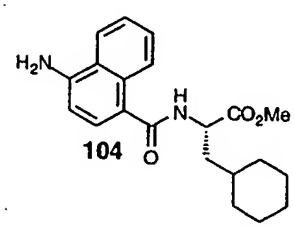
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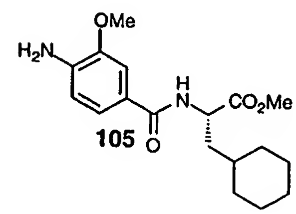
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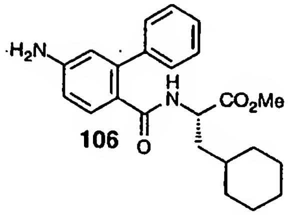
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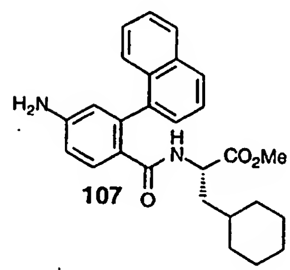
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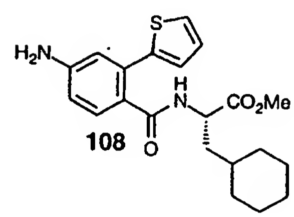
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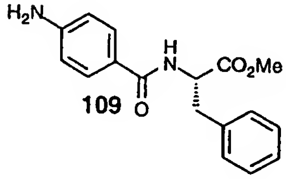
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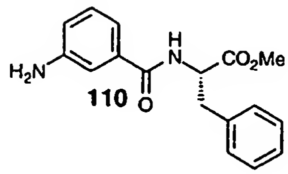
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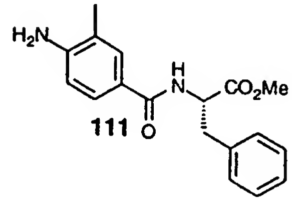
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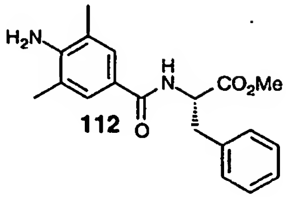
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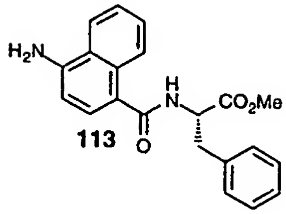
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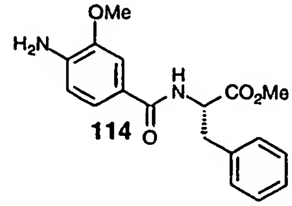
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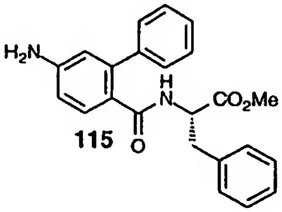
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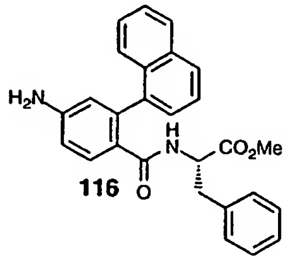
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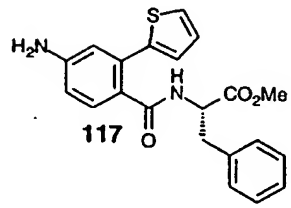
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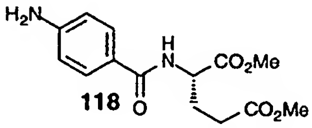
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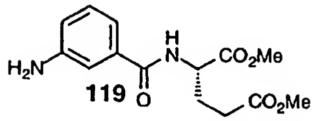
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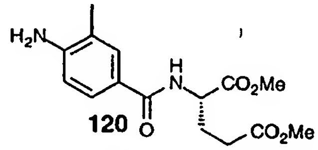
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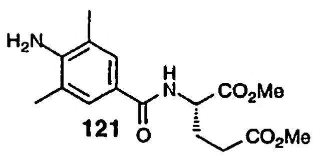
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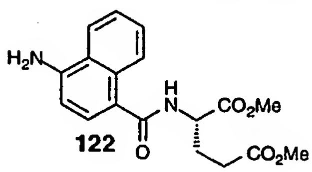
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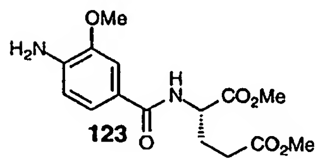
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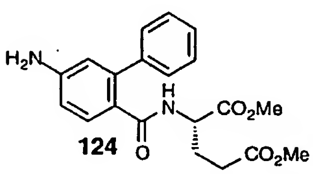
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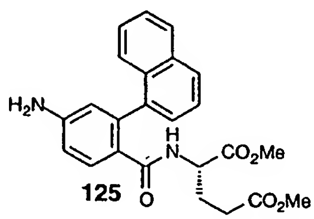
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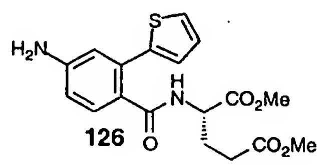
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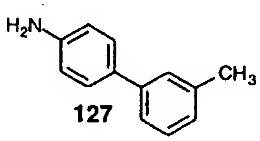
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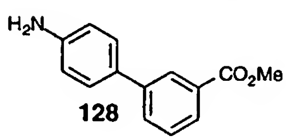
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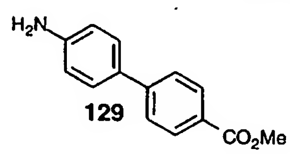
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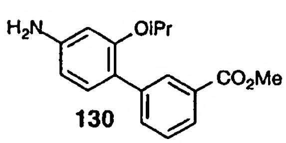
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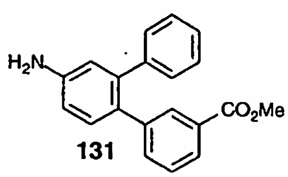
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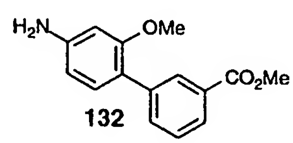
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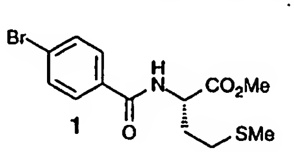
Table 11. Bromides of the type B-Br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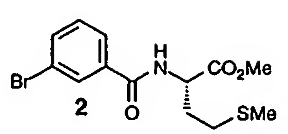
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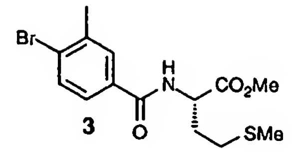
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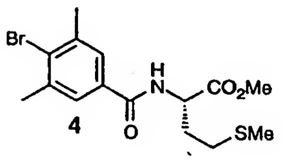
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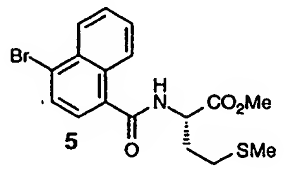
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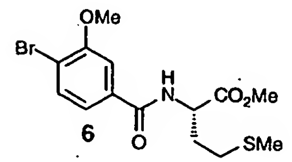
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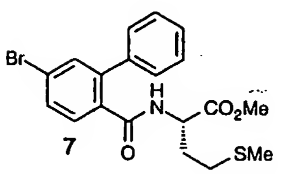
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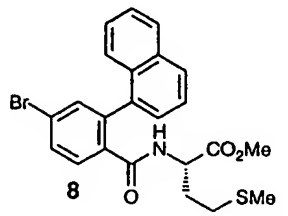
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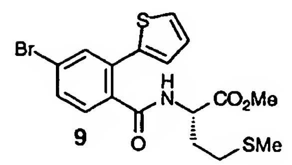
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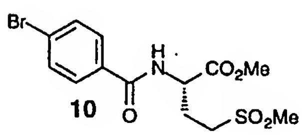
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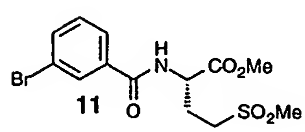
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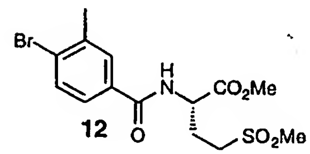
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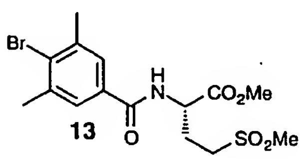
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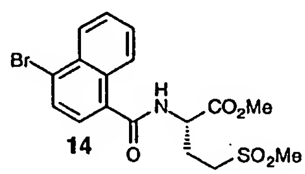
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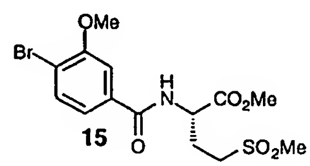
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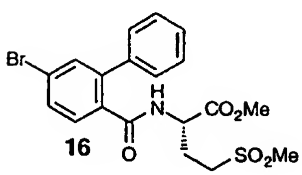
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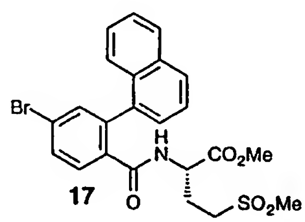
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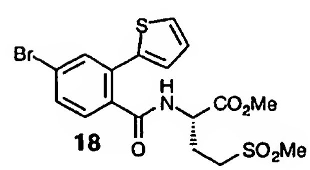
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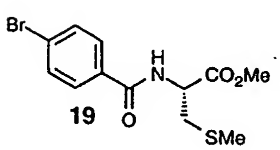
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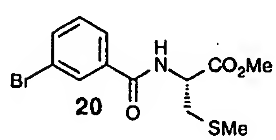
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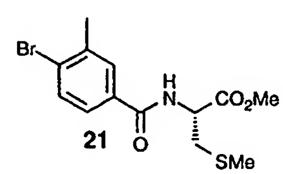
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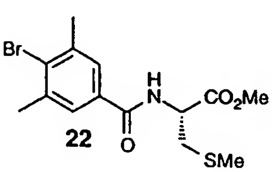
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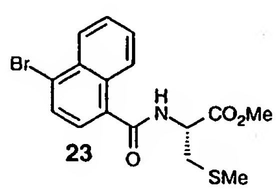
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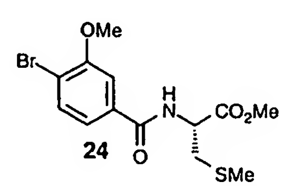
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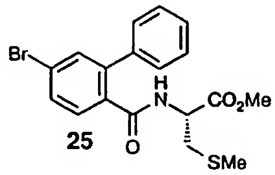
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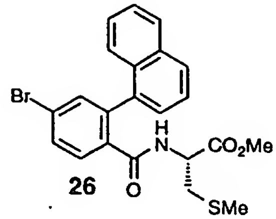
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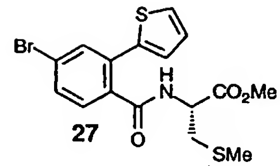
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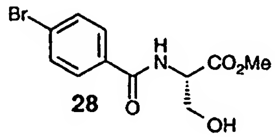
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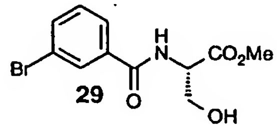
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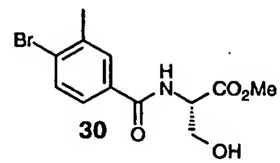
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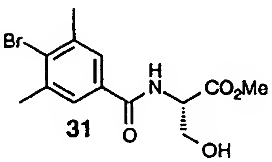
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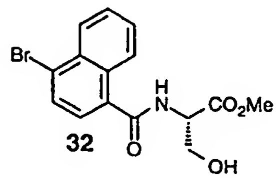
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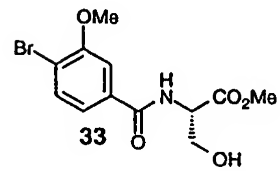
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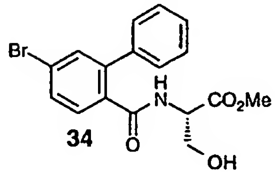
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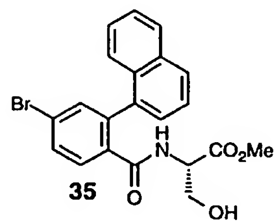
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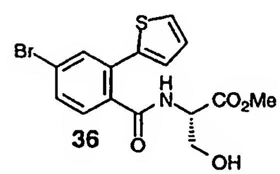
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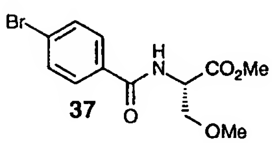
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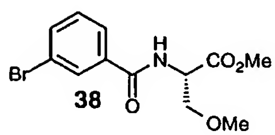
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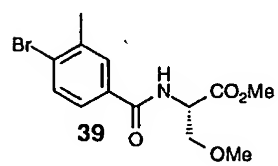
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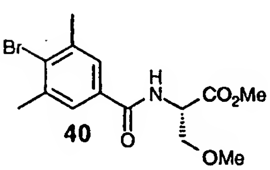
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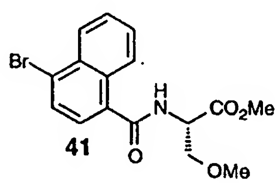
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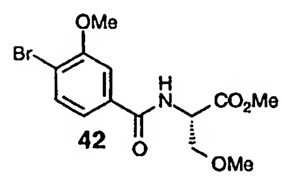
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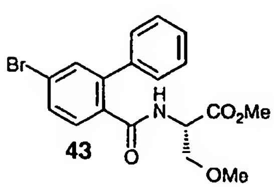
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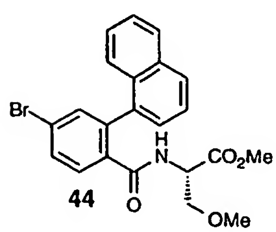
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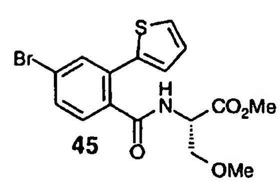
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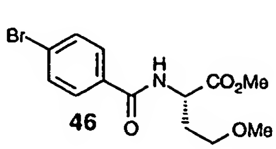
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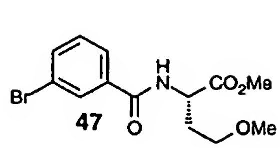
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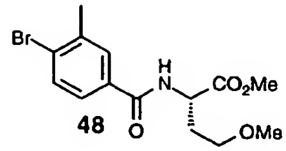
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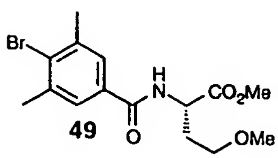
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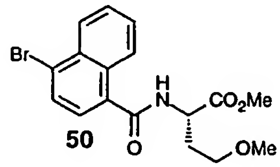
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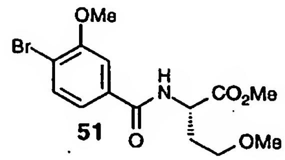
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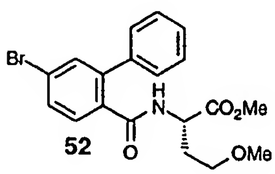
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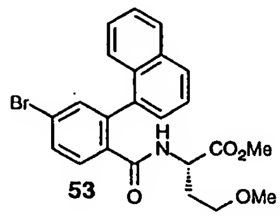
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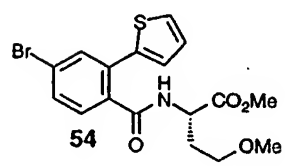
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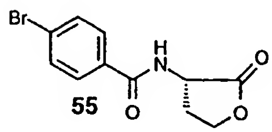
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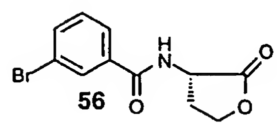
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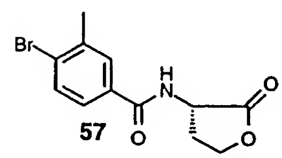
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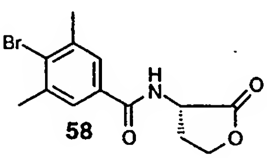
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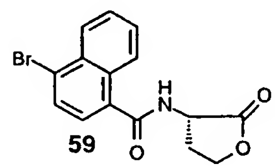
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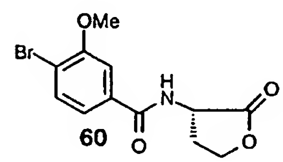
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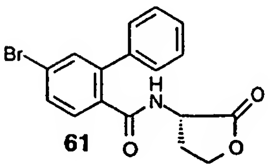
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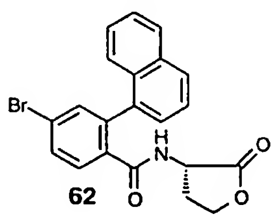
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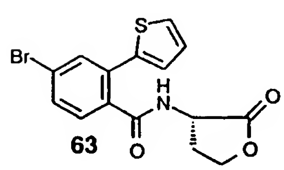
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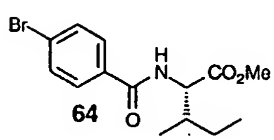
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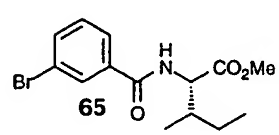
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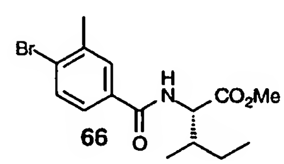
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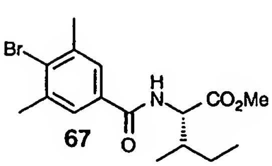
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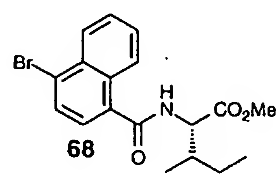
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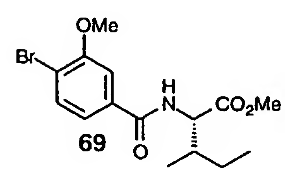
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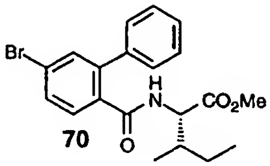
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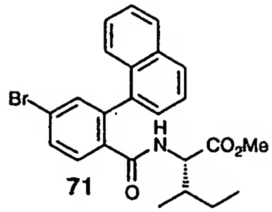
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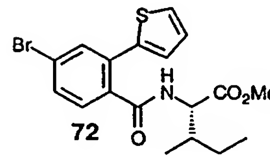
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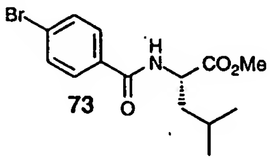
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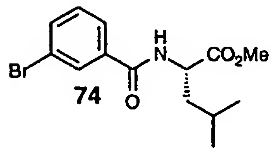
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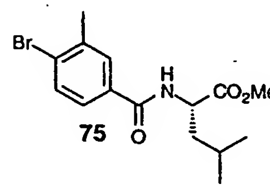
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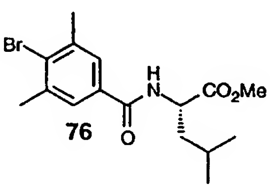
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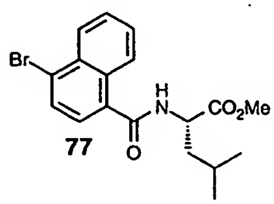
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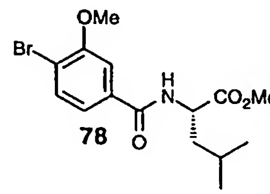
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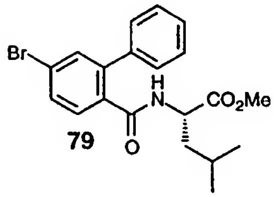
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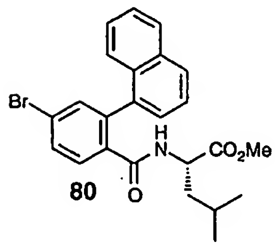
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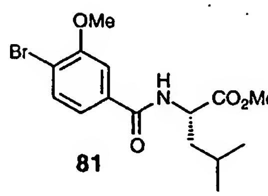
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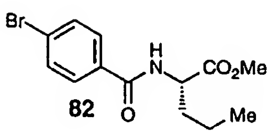
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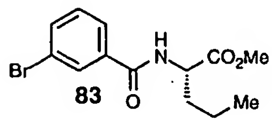
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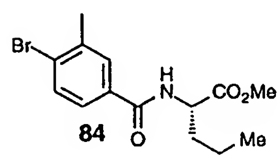
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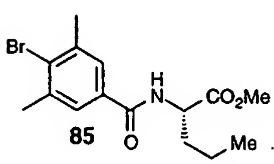
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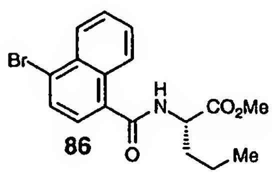
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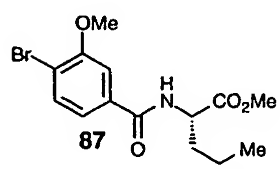
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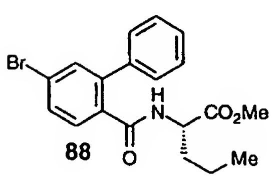
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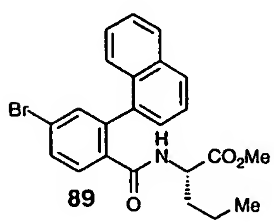
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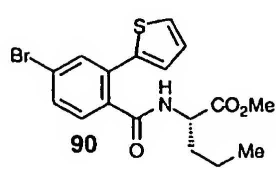
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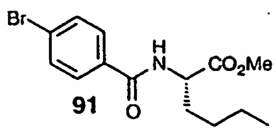
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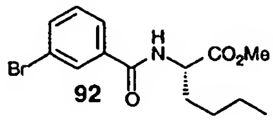
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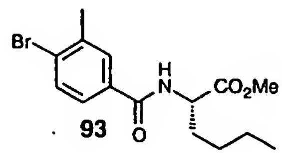
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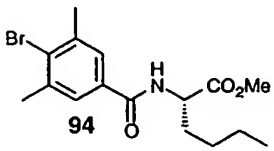
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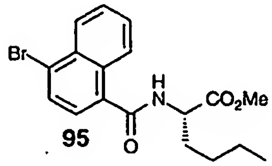
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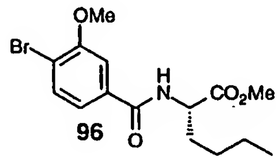
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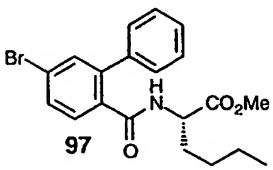
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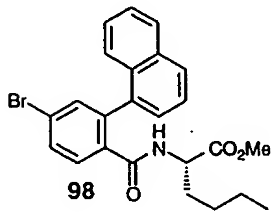
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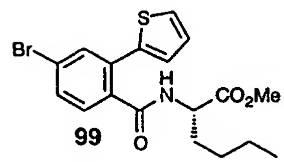
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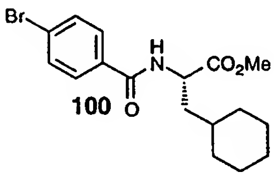
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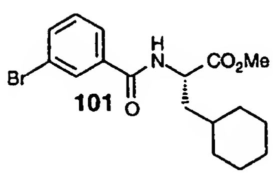
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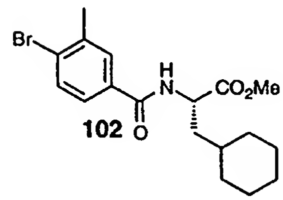
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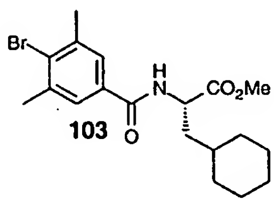
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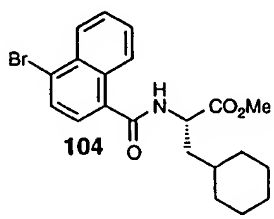
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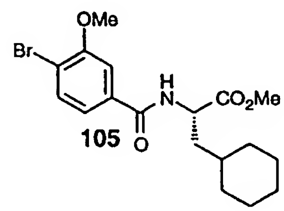
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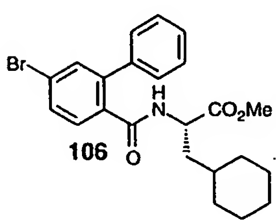
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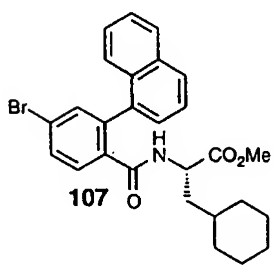
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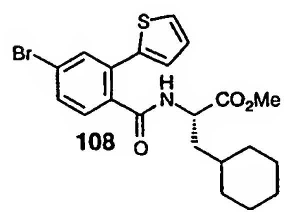
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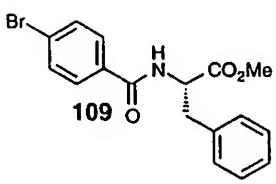
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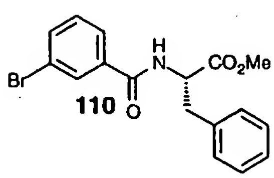
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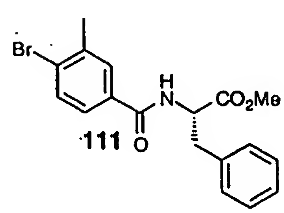
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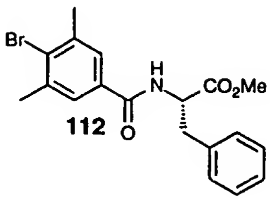
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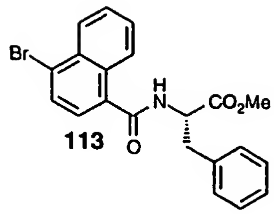
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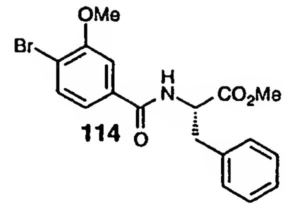
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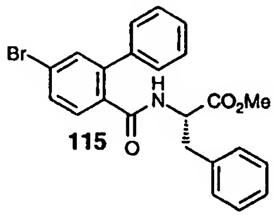
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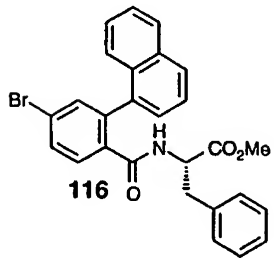
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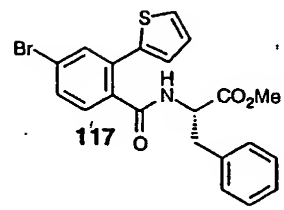
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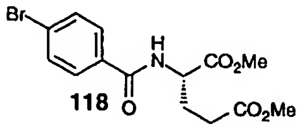
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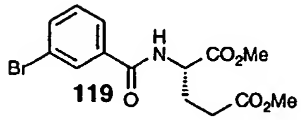
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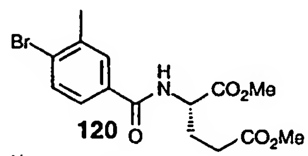
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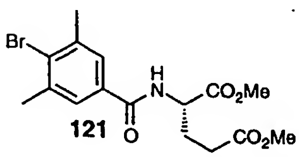
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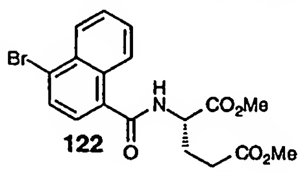
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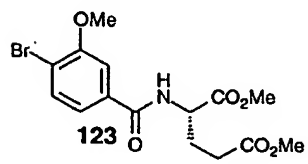
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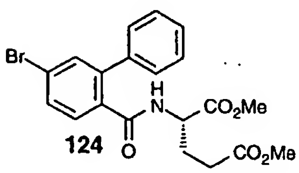
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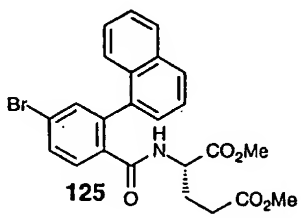
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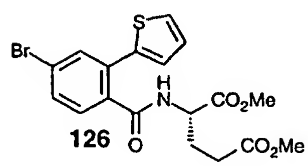
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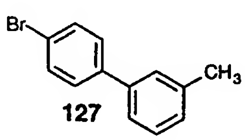
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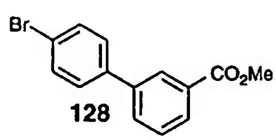
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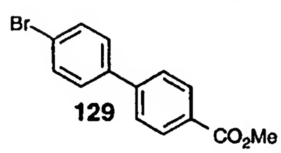
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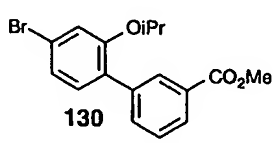
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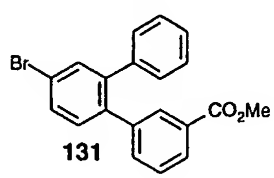
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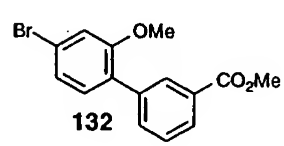
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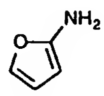
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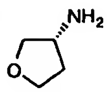
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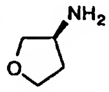
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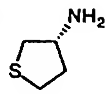
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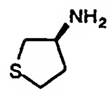
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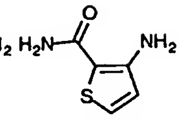
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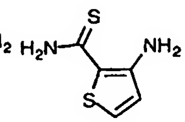
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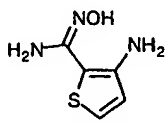
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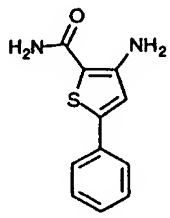
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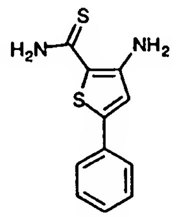
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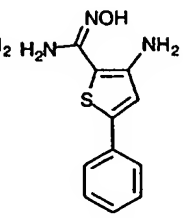
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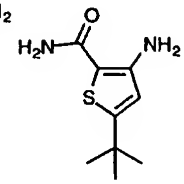
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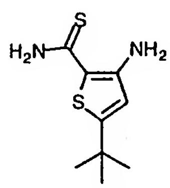
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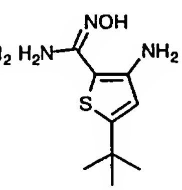
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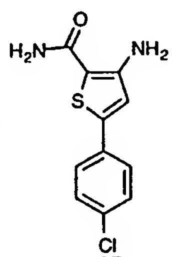
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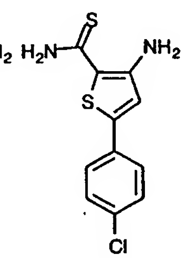
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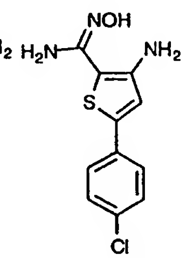
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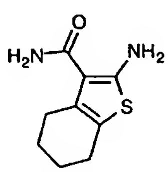
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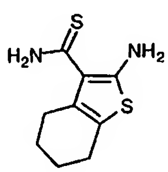
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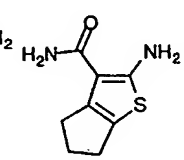
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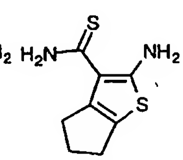
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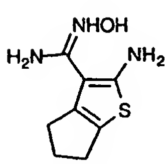
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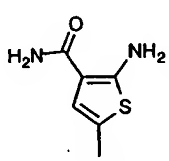
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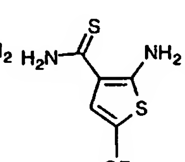
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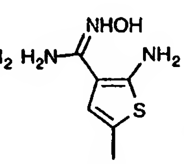
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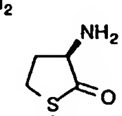
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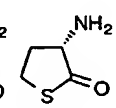
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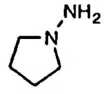
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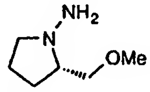
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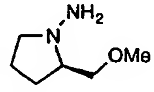
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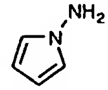
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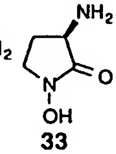
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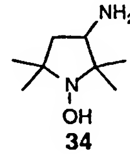
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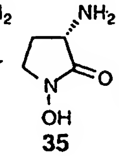
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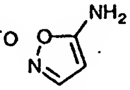
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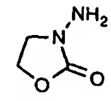
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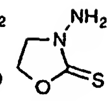
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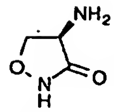
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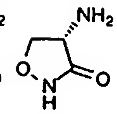
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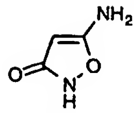
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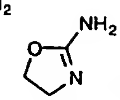
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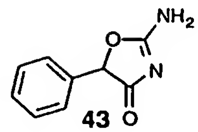
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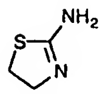
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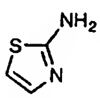
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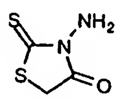
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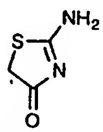
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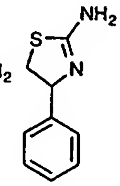
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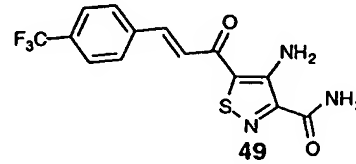
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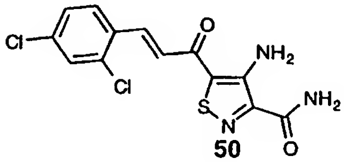
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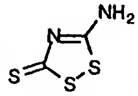
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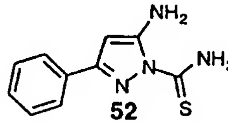
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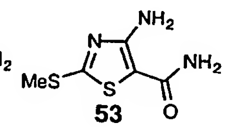
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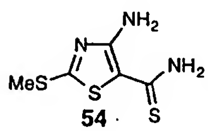
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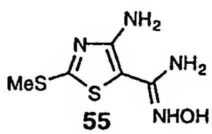
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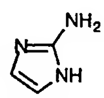
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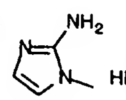
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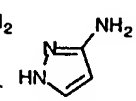
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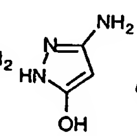
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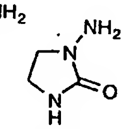
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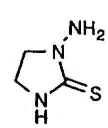
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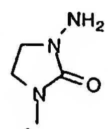
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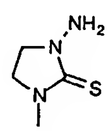
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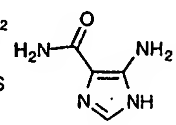
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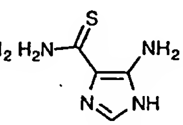
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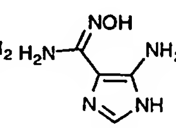
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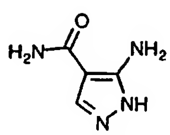
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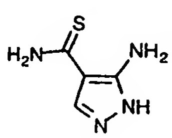
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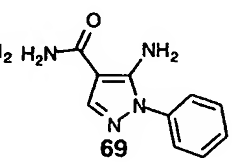
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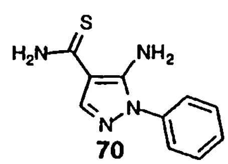
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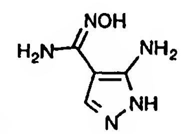
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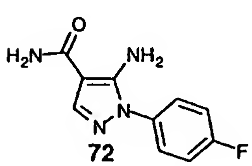
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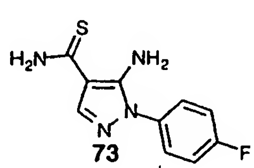
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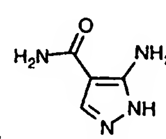
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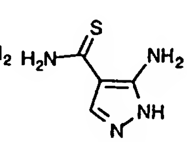
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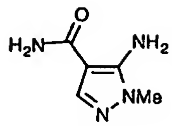
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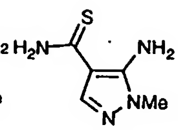
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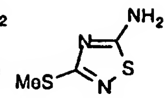
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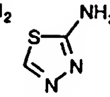
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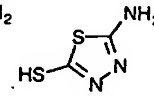
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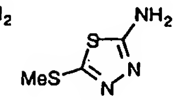
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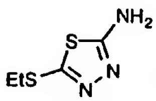
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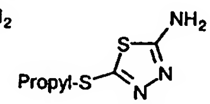
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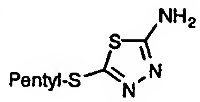
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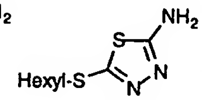
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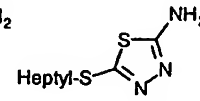
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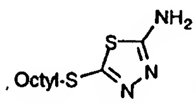
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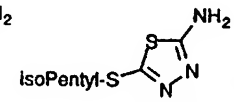
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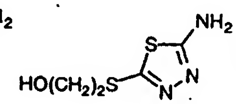
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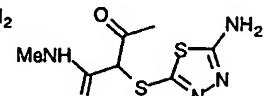
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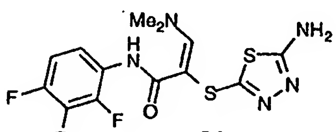
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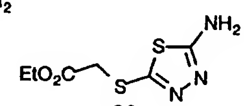
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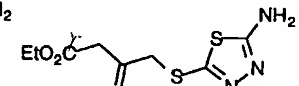
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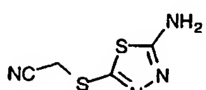
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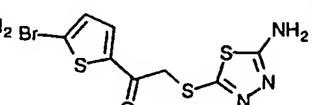
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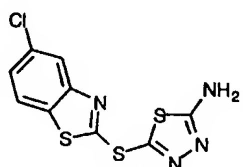
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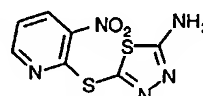
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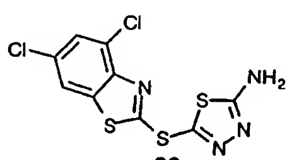
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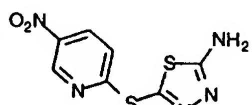
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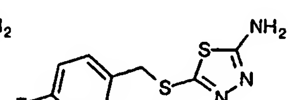
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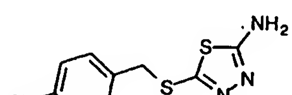
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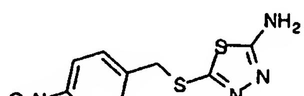
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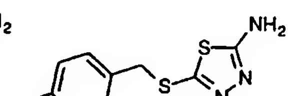
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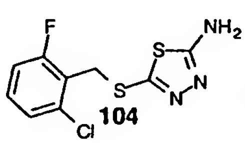
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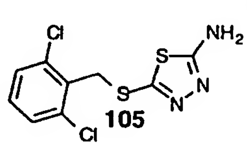
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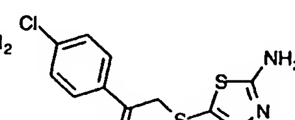
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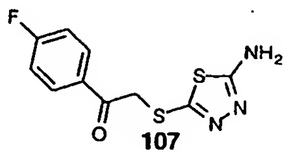
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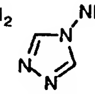
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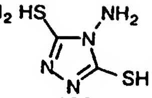
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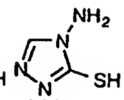
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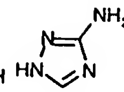
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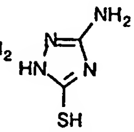
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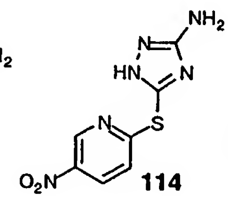
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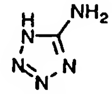
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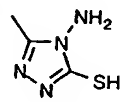
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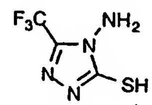
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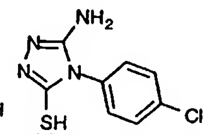
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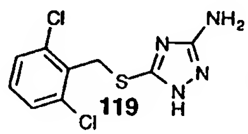
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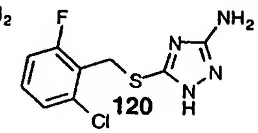
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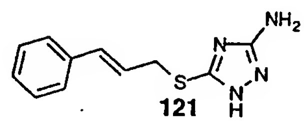
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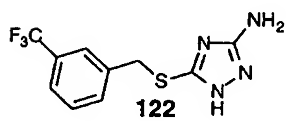
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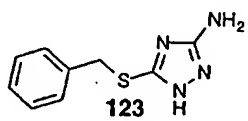
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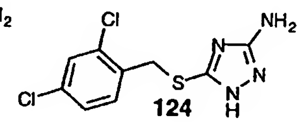
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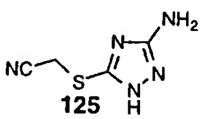
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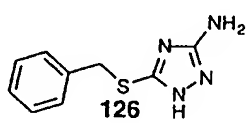
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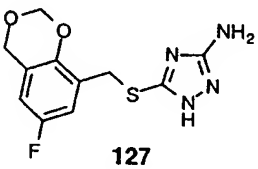
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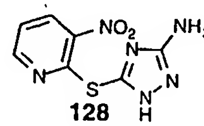
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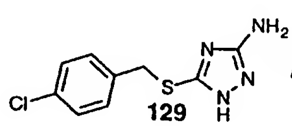
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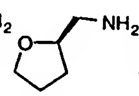
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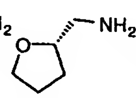
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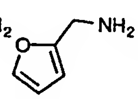
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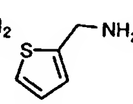
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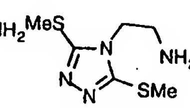
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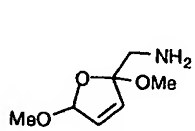
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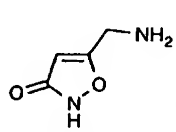
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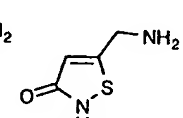
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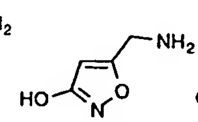
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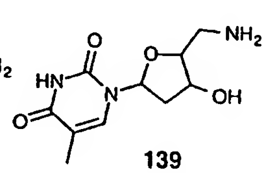
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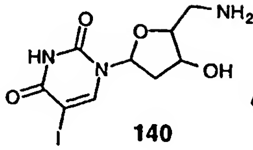
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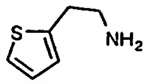
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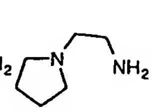
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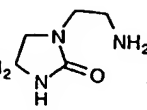
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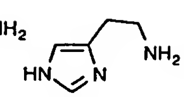
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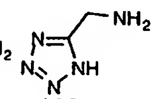
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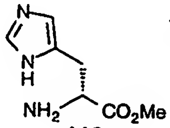
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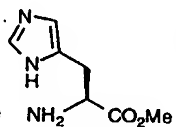
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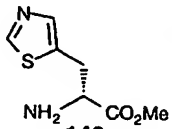
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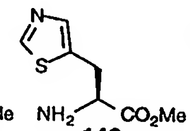
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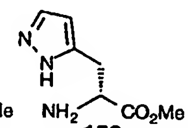
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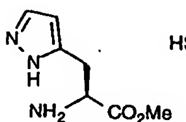
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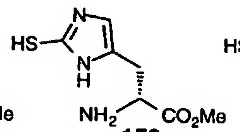
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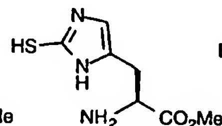
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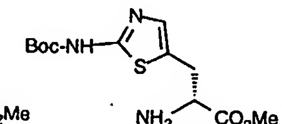
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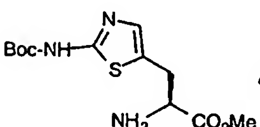
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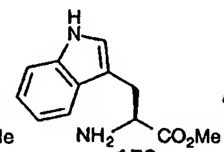
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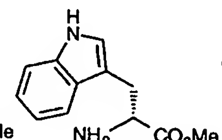
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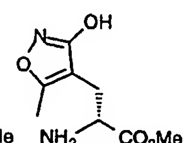
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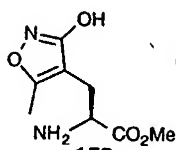
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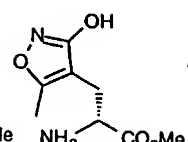
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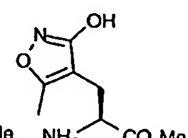
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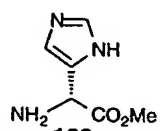
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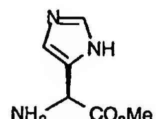
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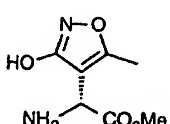
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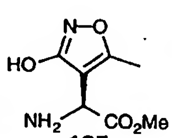
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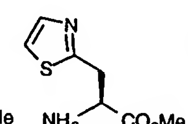
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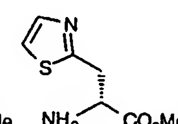
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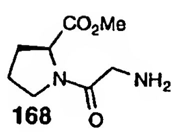
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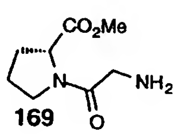
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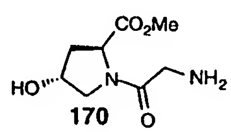
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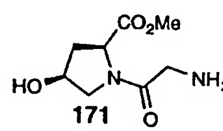
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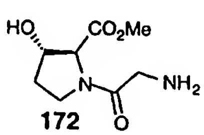
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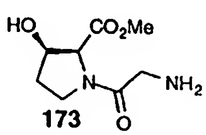
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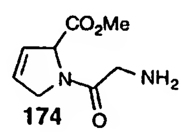
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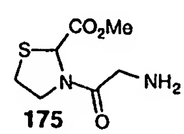
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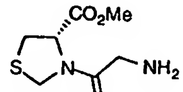
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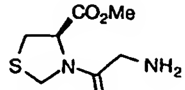
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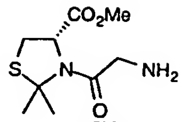
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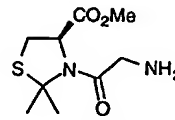
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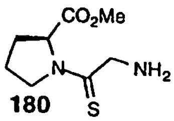
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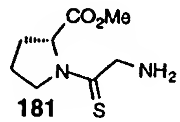
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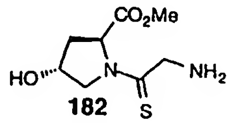
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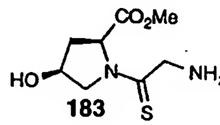
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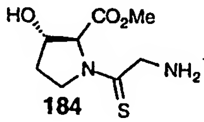
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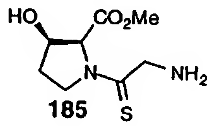
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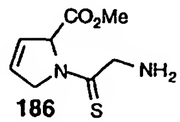
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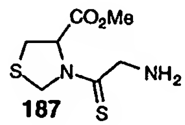
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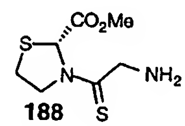
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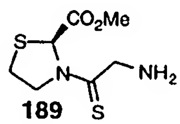
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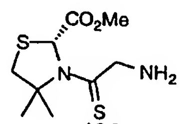
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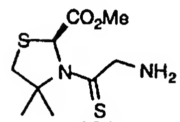
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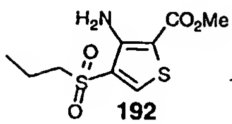
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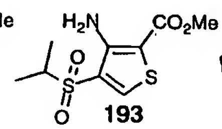
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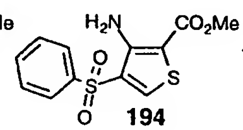
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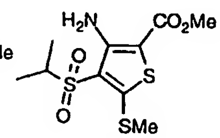
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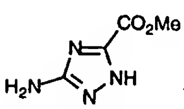
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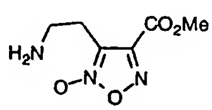
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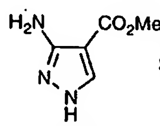
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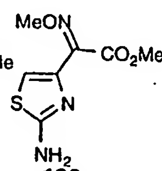
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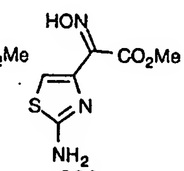
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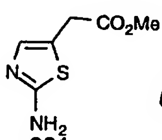
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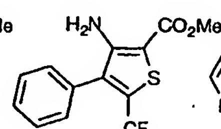
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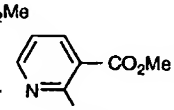
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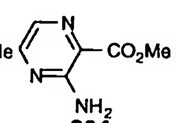
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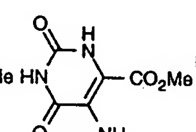
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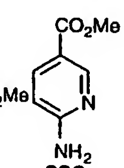
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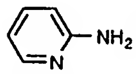
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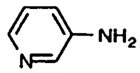
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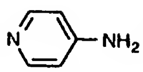
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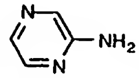
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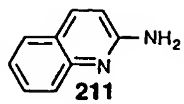
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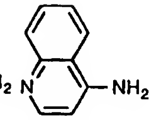
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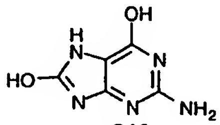
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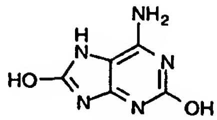
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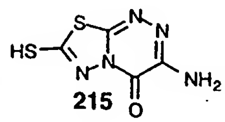
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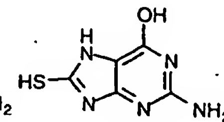
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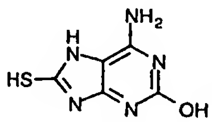
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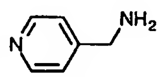
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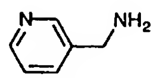
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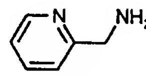
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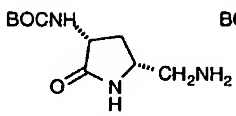
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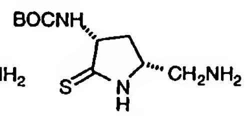
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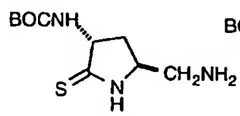
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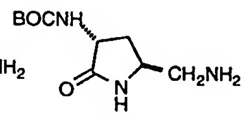
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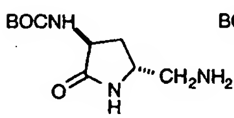
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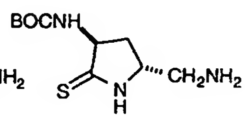
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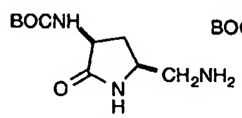
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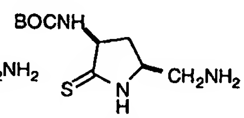
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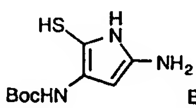
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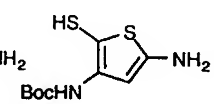
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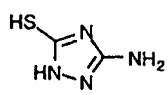
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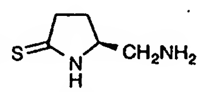
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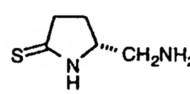
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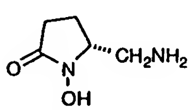
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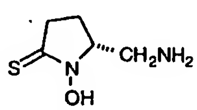
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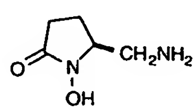
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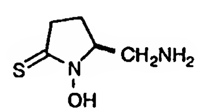
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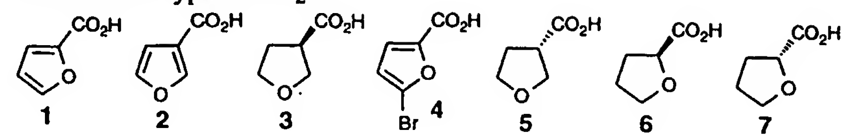

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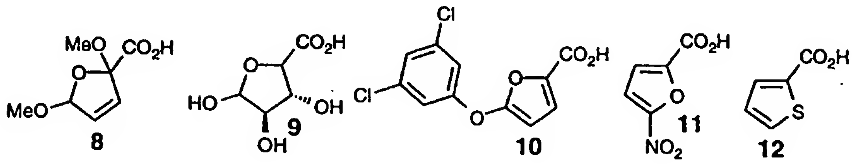

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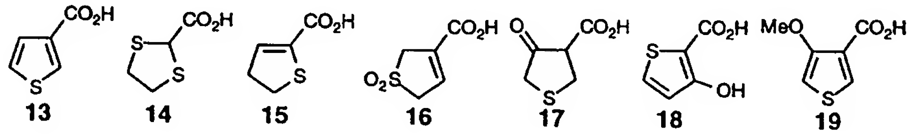

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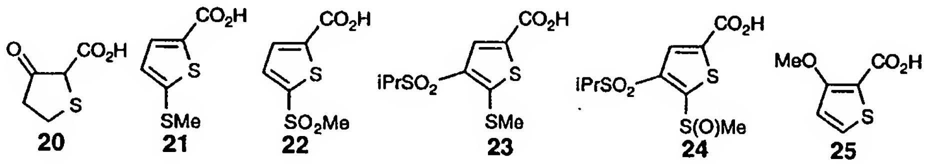

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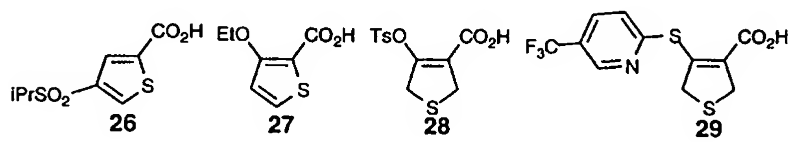

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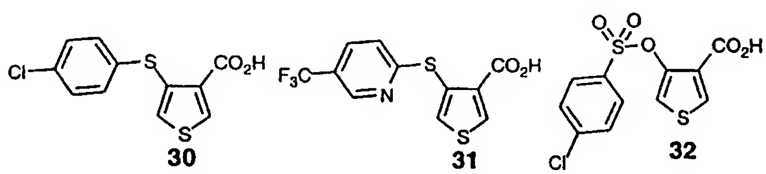

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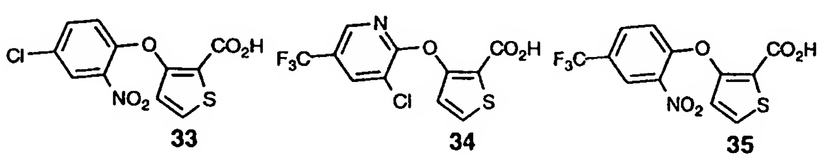

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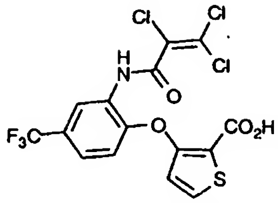
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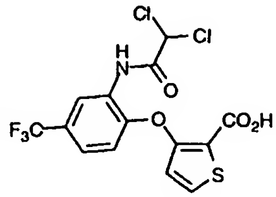
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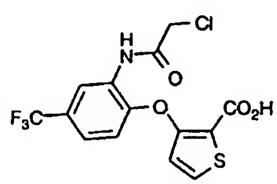
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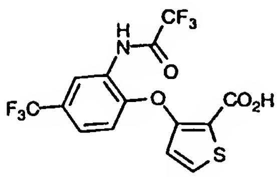
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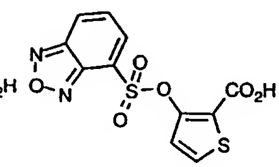
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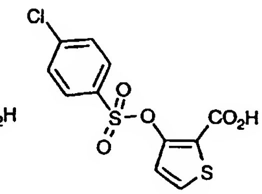
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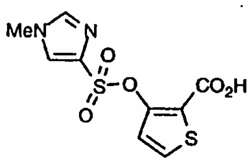
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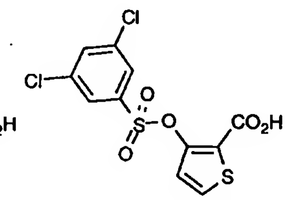
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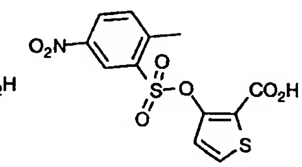
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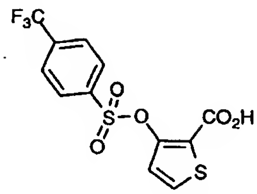
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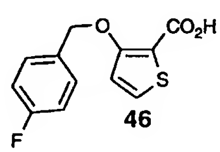
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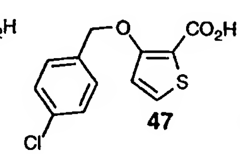
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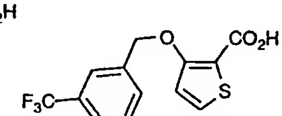
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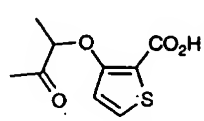
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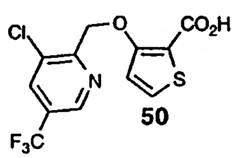
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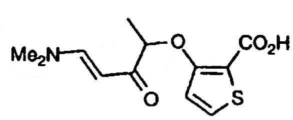
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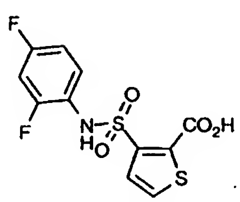
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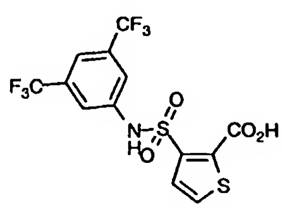
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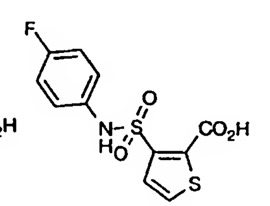
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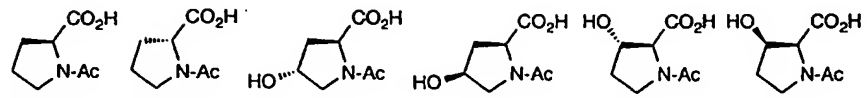

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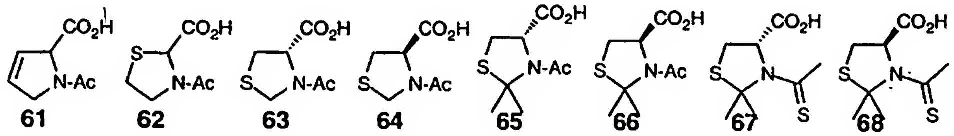

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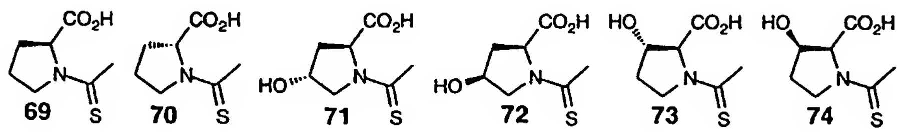

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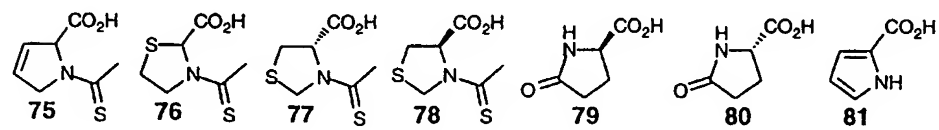

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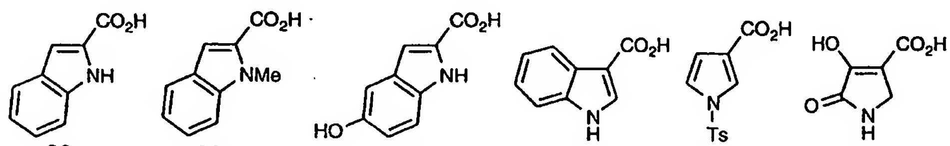

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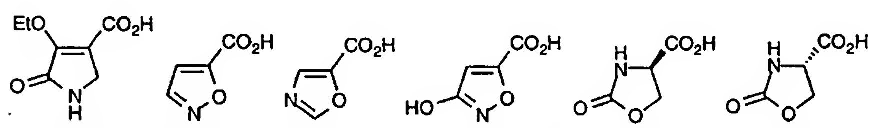

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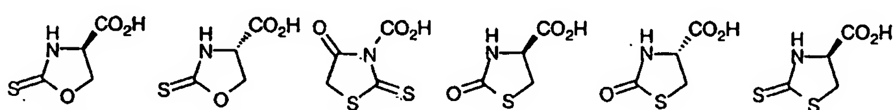

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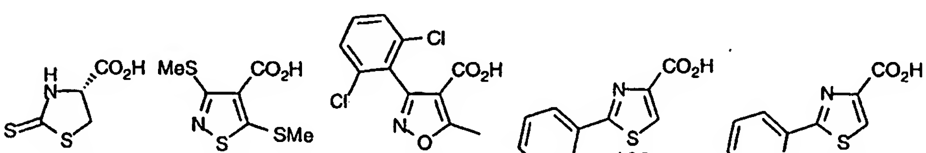

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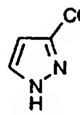
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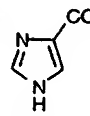
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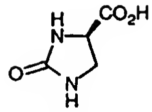
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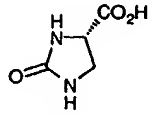
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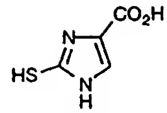
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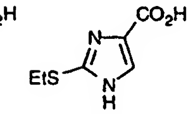
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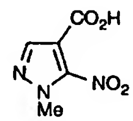
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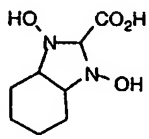
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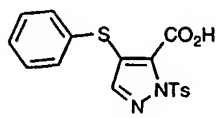
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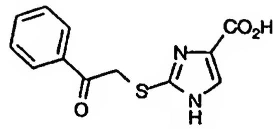
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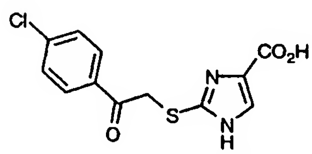
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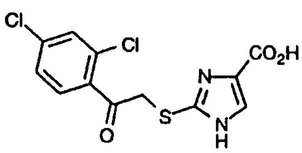
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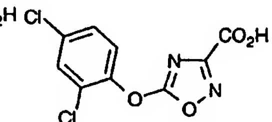
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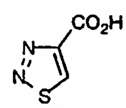
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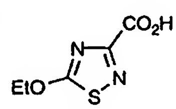
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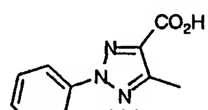
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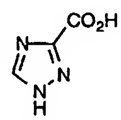
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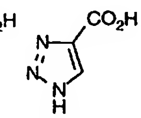
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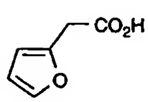
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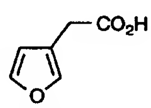
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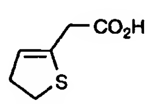
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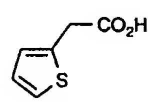
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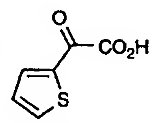
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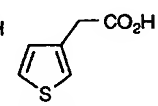
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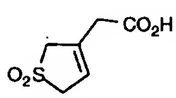
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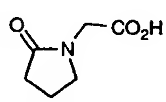
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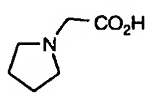
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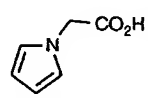
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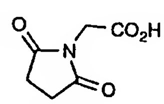
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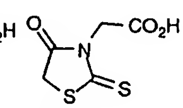
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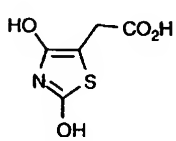
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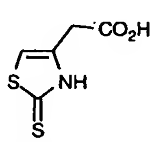
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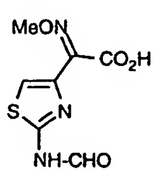
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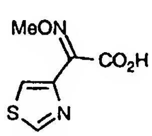
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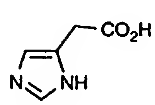
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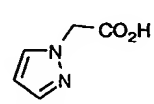
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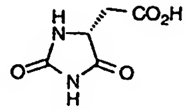
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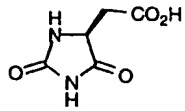
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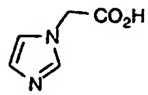
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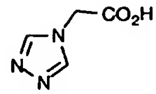
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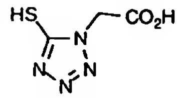
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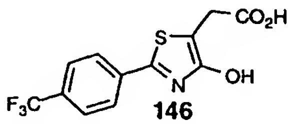
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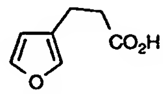
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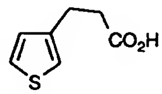
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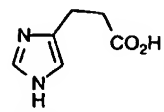
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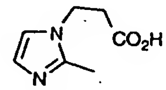
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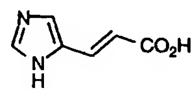
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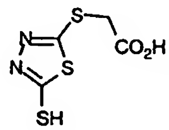
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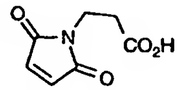
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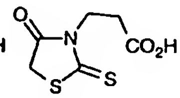
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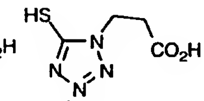
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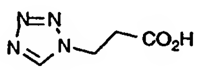
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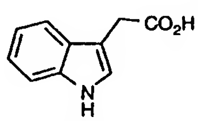
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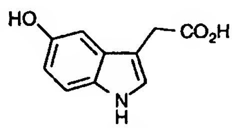
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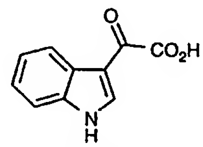
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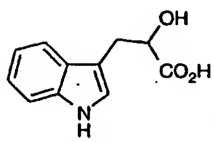
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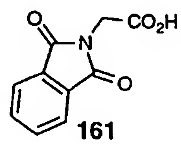
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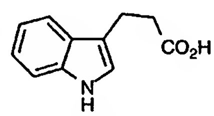
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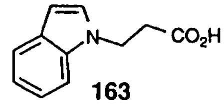
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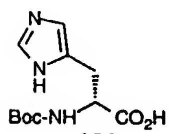
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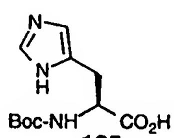
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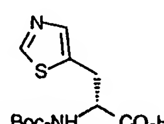
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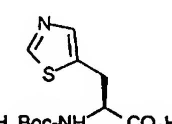
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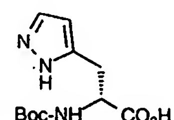
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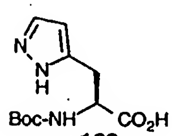
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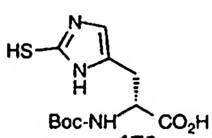
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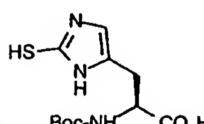
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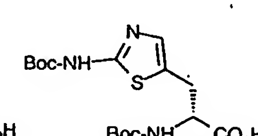
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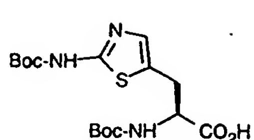
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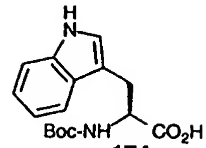
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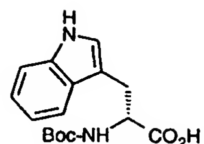
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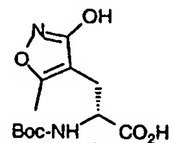
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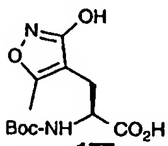
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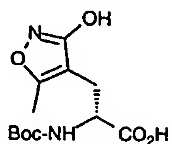
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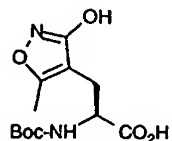
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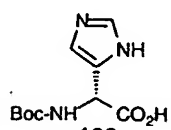
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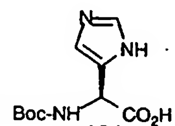
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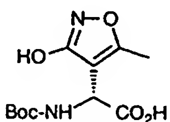
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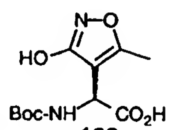
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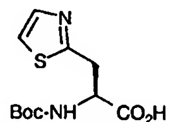
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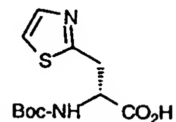
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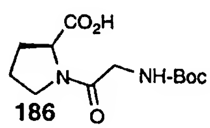
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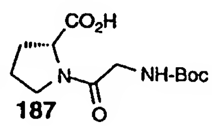
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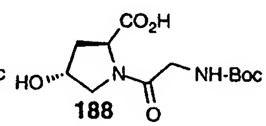
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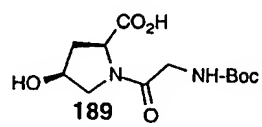
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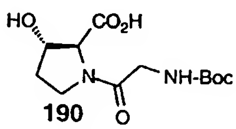
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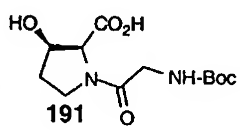
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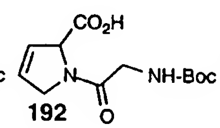
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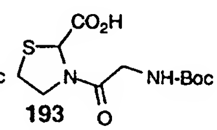
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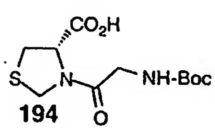
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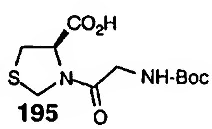
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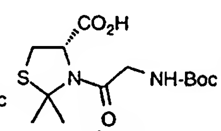
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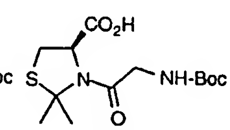
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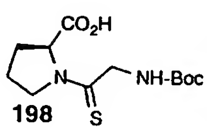
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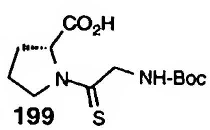
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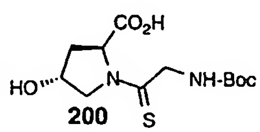
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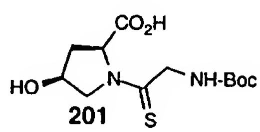
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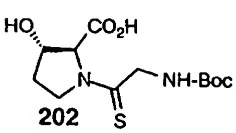
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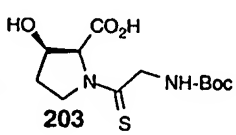
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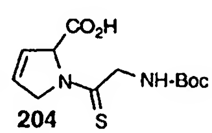
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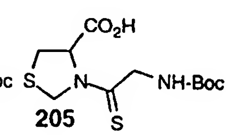
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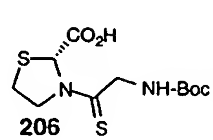
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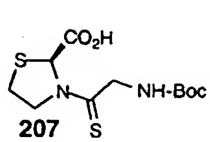
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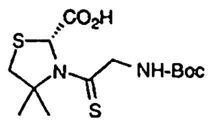
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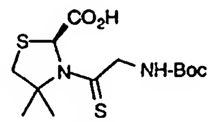
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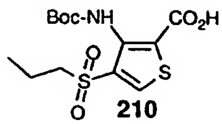
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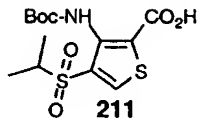
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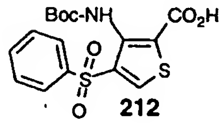
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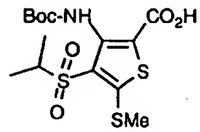
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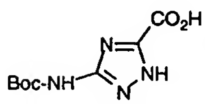
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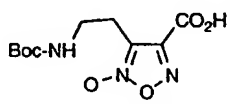
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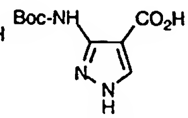
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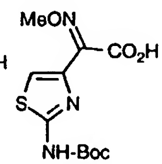
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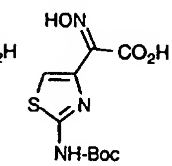
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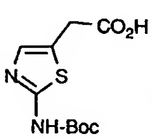
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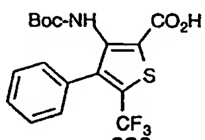
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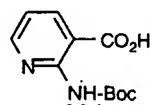
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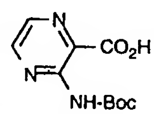
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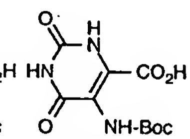
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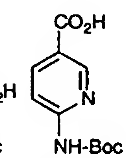
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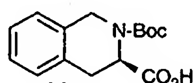
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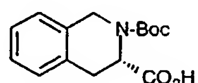
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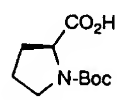
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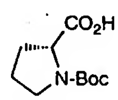
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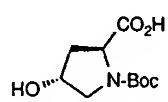
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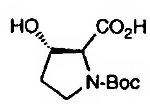
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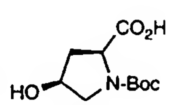
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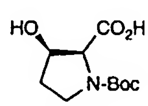
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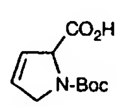
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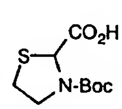
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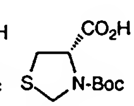
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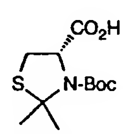
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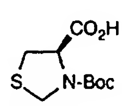
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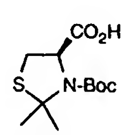
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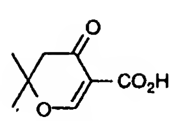
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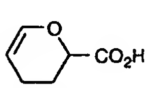
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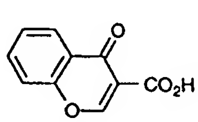
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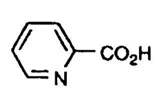
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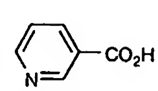
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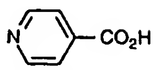
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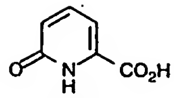
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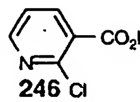
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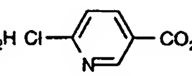
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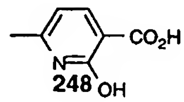
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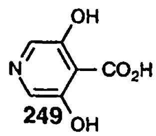
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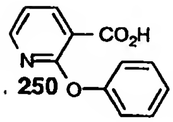
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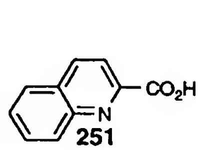
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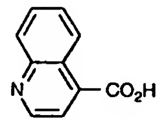
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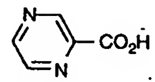
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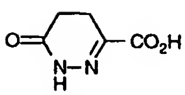
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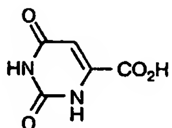
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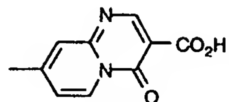
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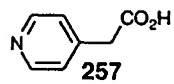
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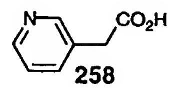
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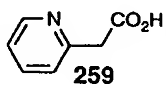
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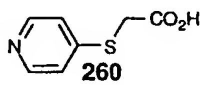
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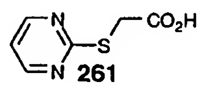
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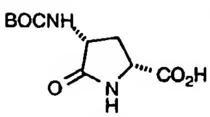
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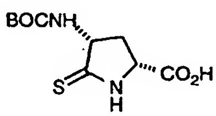
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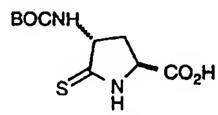
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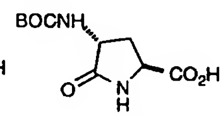
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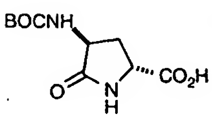
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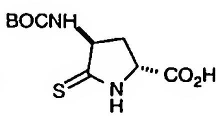
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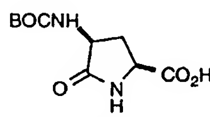
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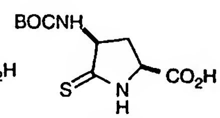
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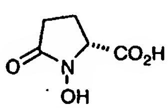
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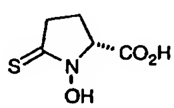
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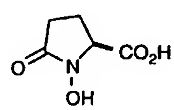
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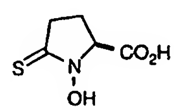
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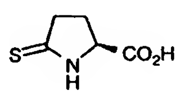
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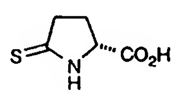
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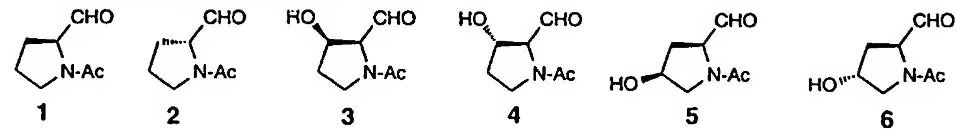

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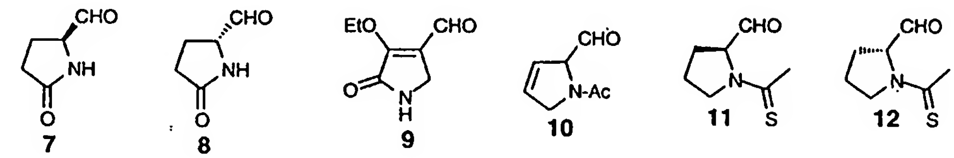

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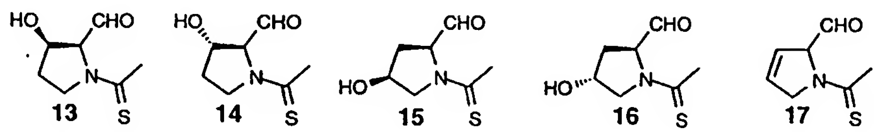

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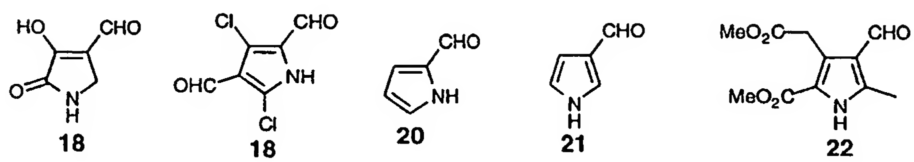

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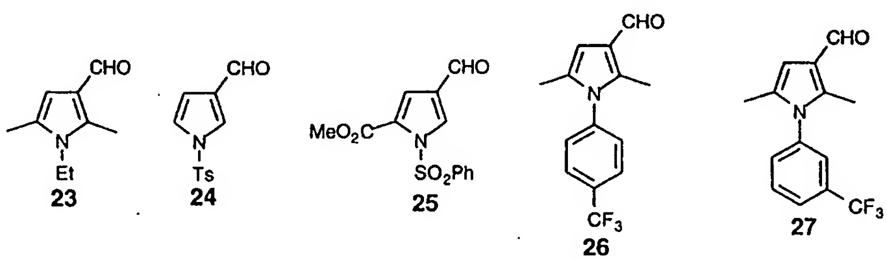

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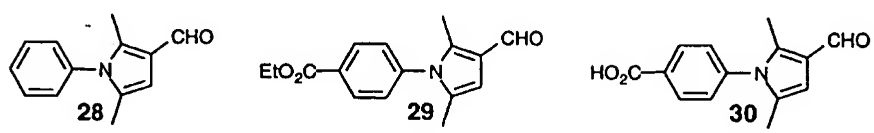

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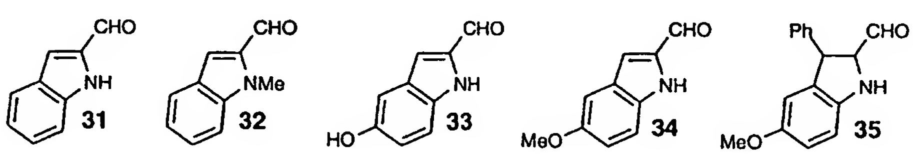

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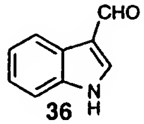
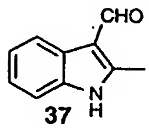
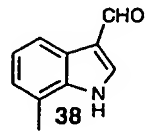
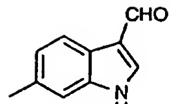
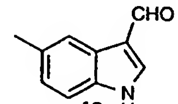
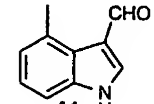
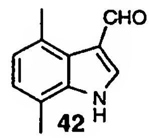
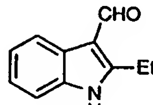
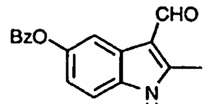
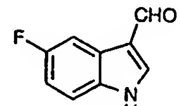
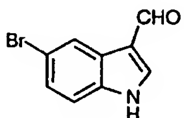
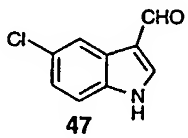
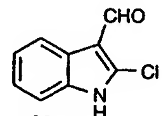
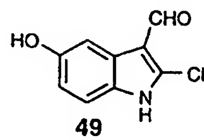
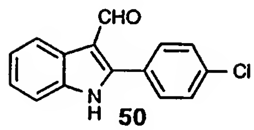
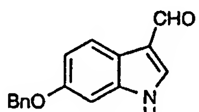
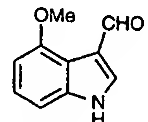
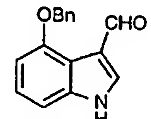
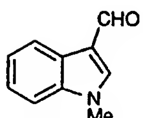
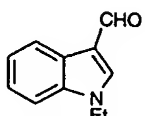
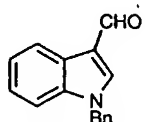
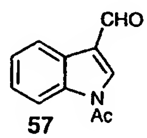
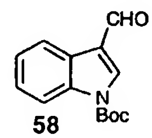
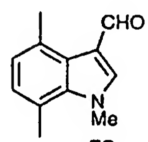
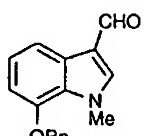
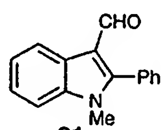
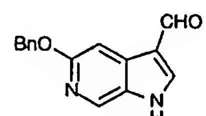
 36
 37
 38
 39
 40

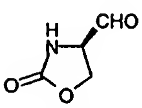
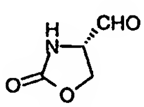
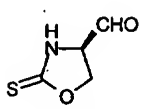
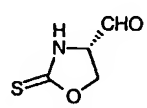
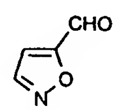
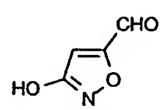
 41
 42
 43
 44
 45

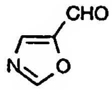
 46
 47
 48
 49

 50
 51
 52
 53

 54
 55
 56
 57
 58

 59
 60
 61
 62

 63
 64
 65
 66
 67
 68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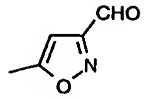
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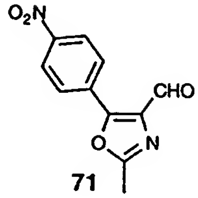
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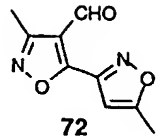
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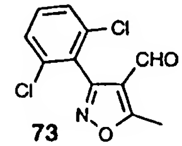
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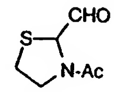
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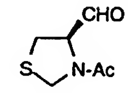
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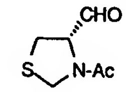
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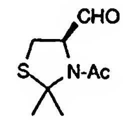
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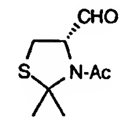
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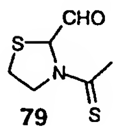
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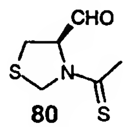
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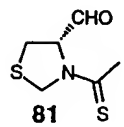
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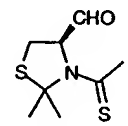
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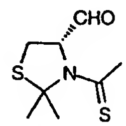
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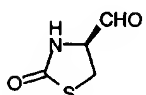
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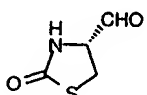
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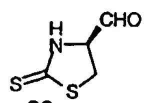
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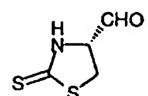
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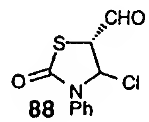
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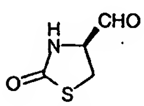
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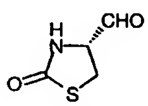
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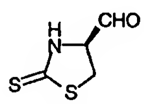
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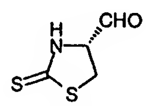
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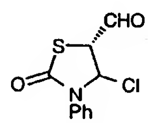
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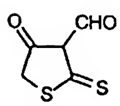
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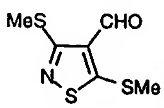
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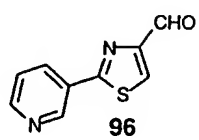
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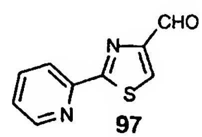
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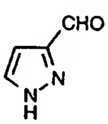
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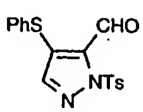
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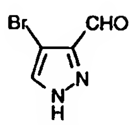
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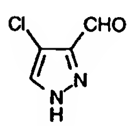
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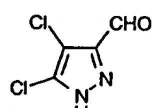
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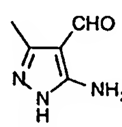
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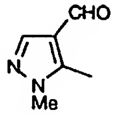
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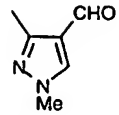
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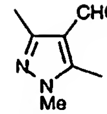
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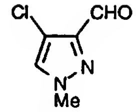
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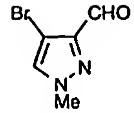
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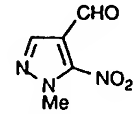
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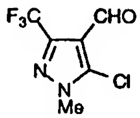
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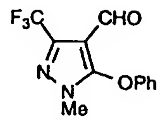
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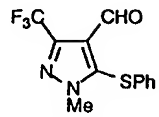
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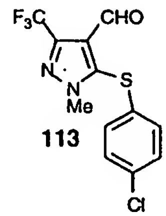
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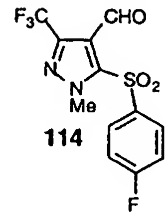
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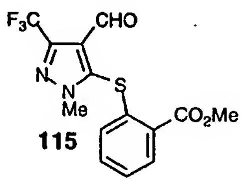
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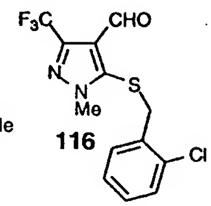
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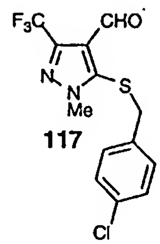
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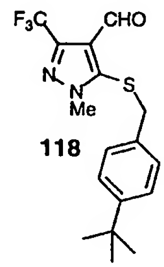
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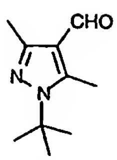
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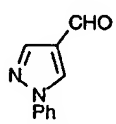
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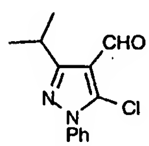
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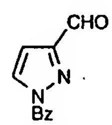
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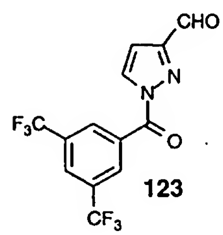
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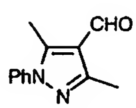
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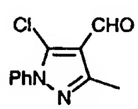
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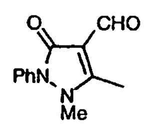
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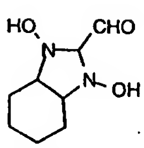
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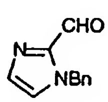
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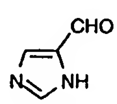
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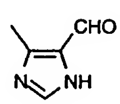
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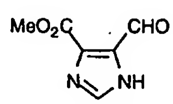
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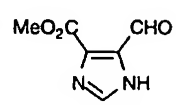
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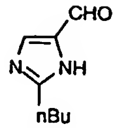
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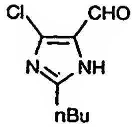
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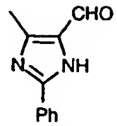
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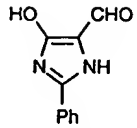
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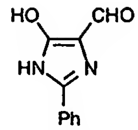
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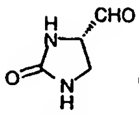
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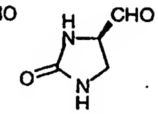
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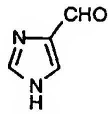
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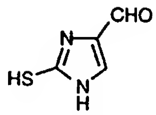
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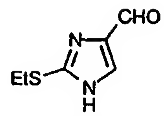
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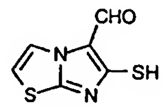
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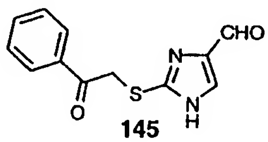
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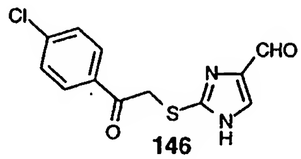
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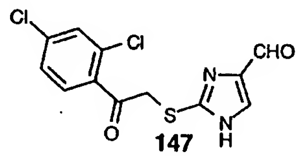
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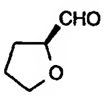
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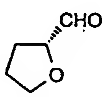
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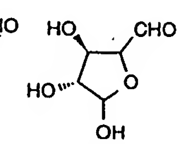
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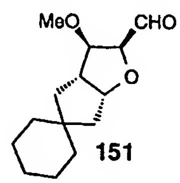
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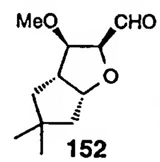
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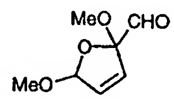
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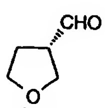
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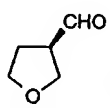
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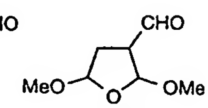
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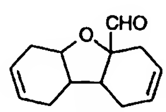
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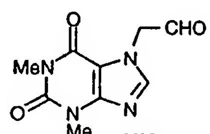
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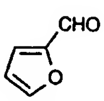
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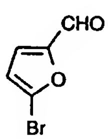
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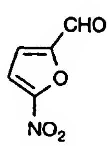
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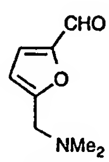
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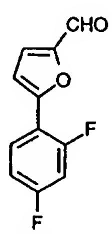
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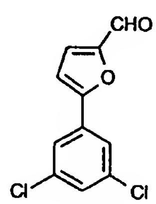
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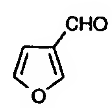
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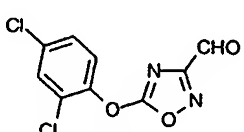
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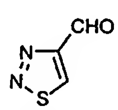
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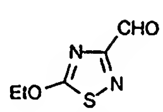
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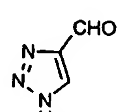
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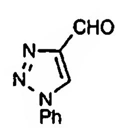
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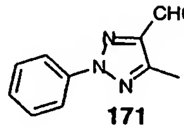
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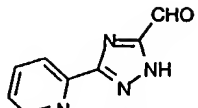
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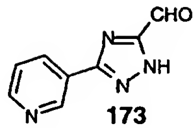
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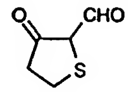
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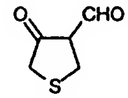
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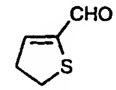
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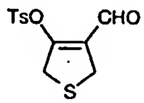
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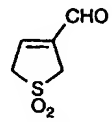
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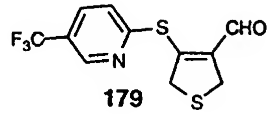
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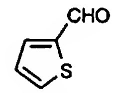
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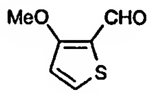
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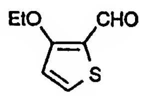
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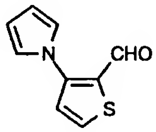
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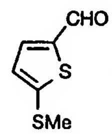
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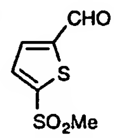
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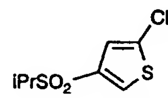
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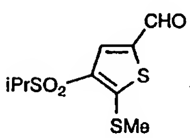
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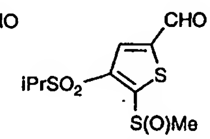
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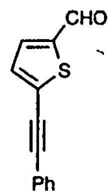
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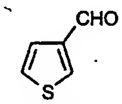
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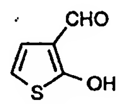
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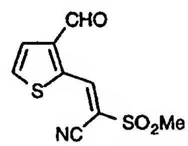
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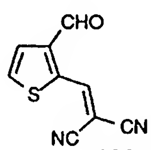
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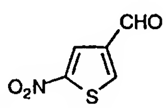
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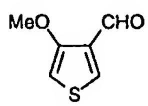
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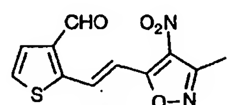
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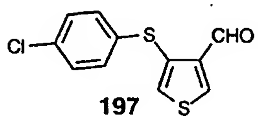
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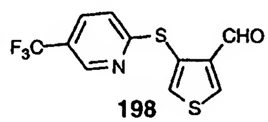
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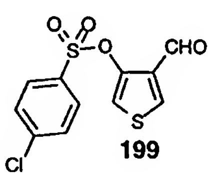
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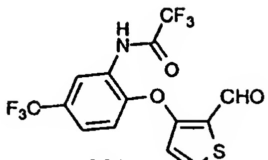
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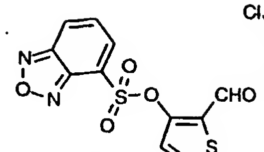
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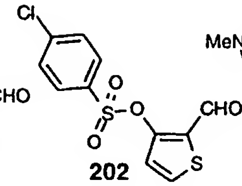
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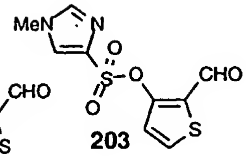
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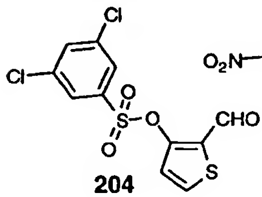
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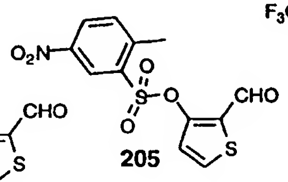
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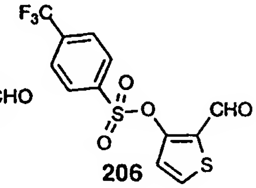
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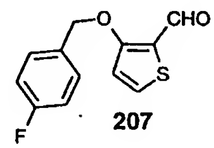
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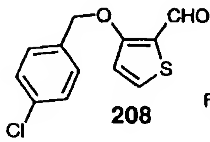
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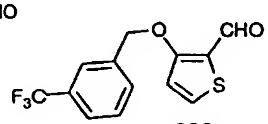
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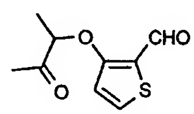
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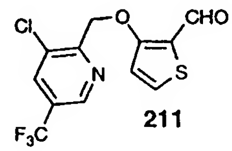
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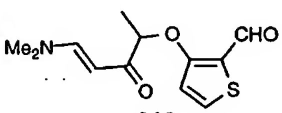
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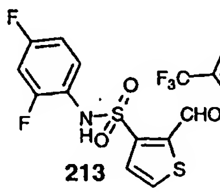
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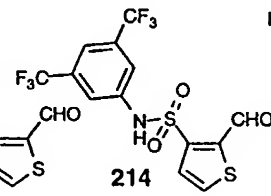
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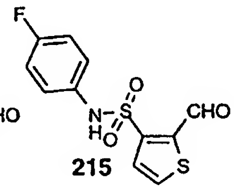
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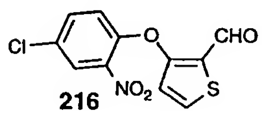
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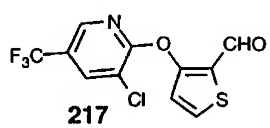
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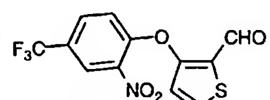
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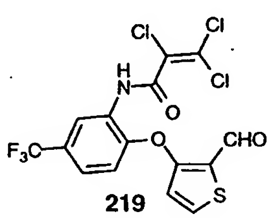
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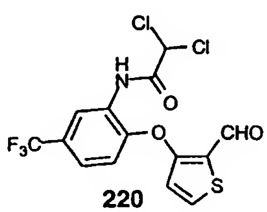
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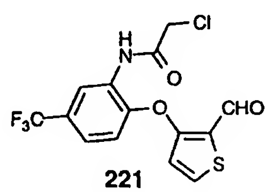
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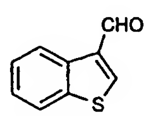
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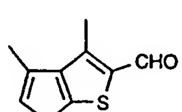
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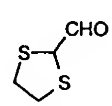
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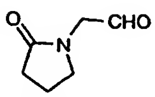
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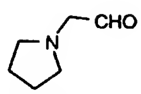
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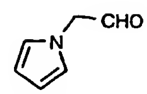
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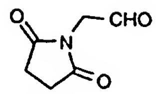
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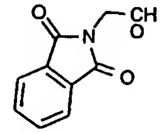
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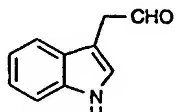
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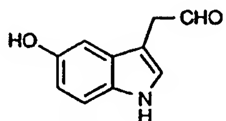
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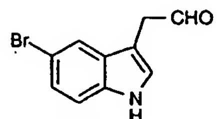
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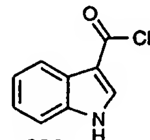
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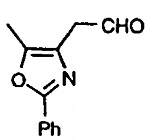
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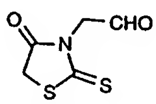
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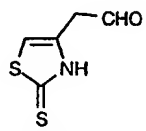
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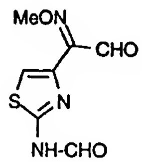
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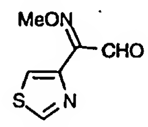
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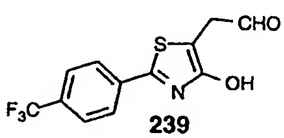
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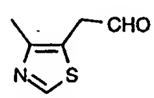
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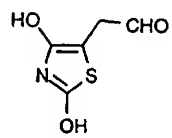
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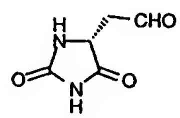
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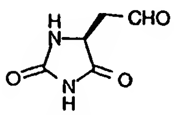
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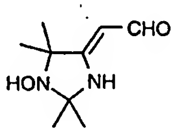
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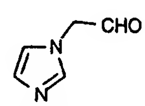
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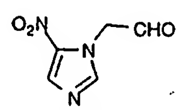
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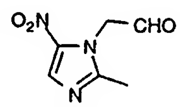
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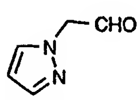
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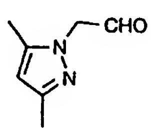
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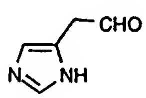
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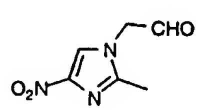
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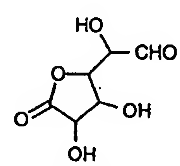
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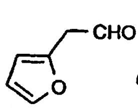
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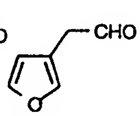
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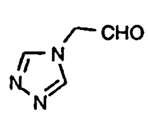
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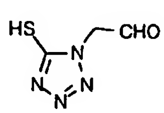
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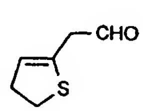
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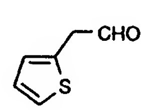
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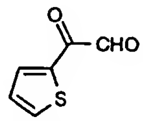
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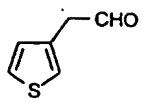
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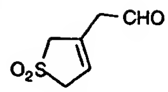
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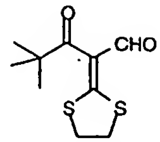
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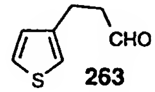
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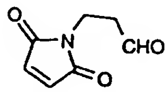
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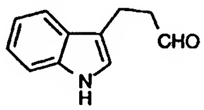
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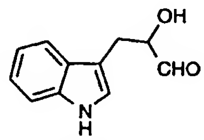
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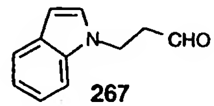
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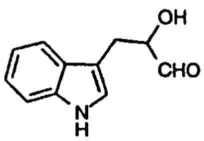
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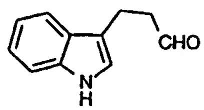
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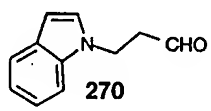
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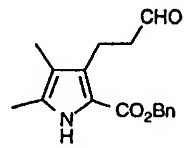
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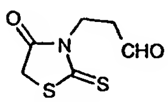
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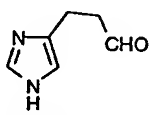
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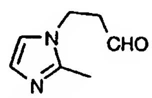
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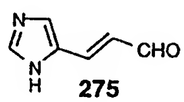
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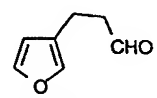
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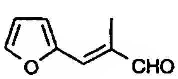
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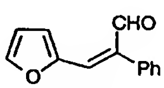
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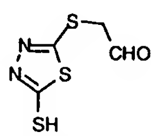
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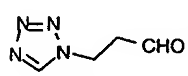
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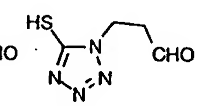
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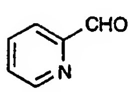
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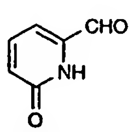
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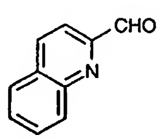
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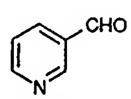
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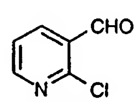
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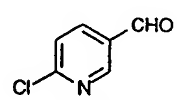
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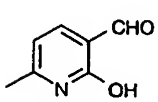
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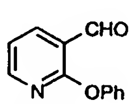
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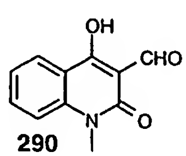
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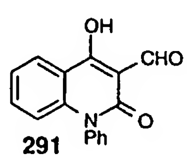
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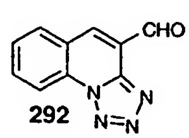
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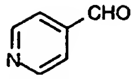
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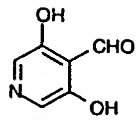
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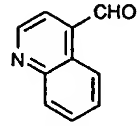
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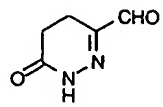
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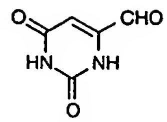
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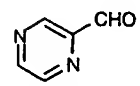
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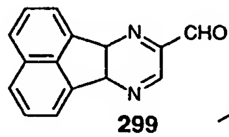
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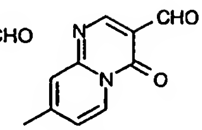
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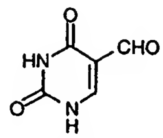
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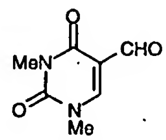
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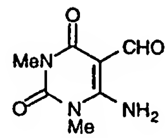
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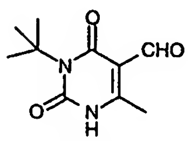
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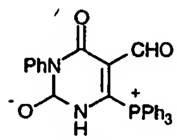
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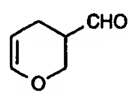
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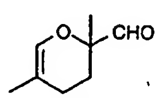
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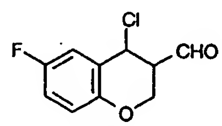
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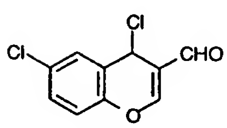
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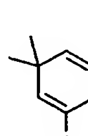
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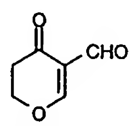
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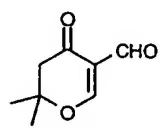
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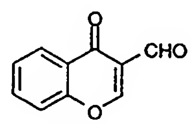
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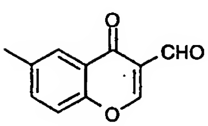
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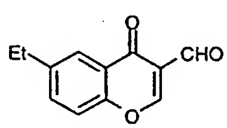
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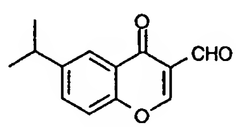
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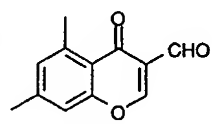
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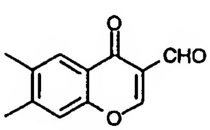
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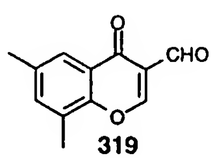
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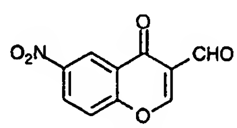
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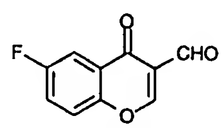
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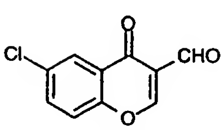
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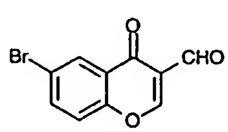
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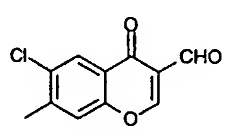
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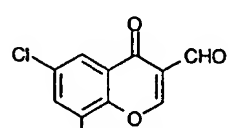
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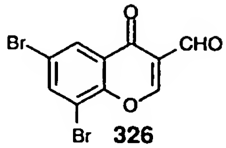
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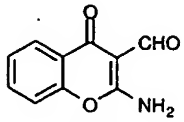
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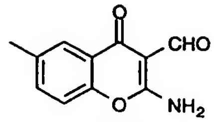
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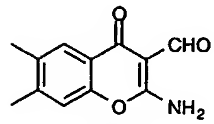
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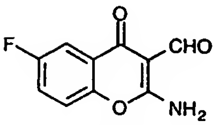
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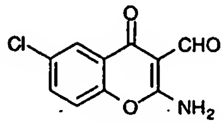
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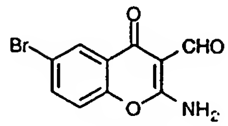
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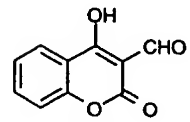
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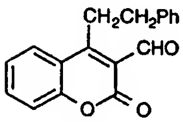
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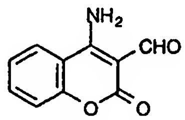
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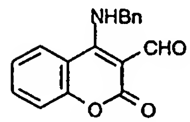
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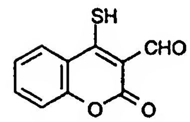
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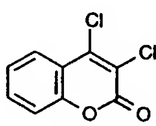
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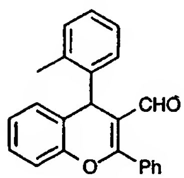
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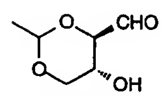
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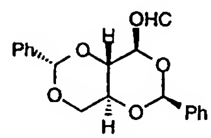
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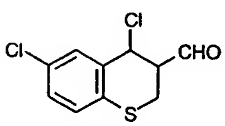
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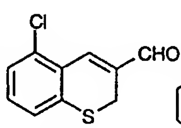
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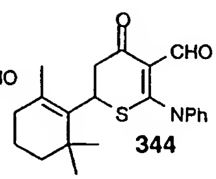
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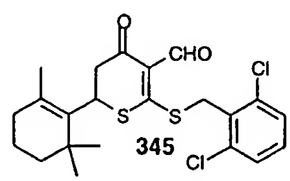
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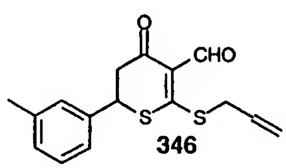
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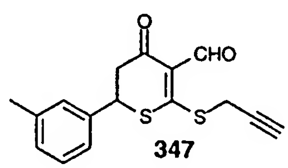
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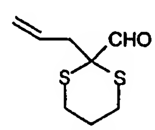
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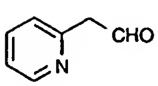
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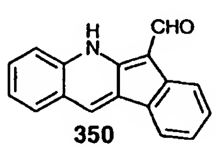
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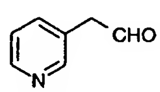
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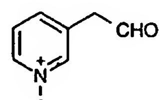
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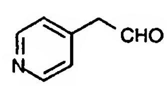
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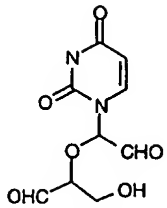
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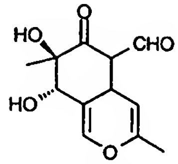
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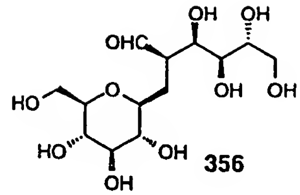
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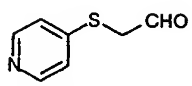
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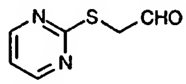
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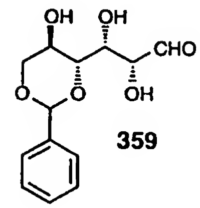
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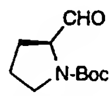
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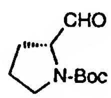
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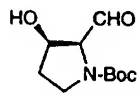
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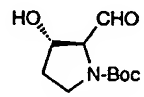
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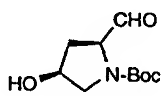
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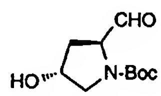
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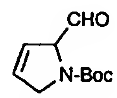
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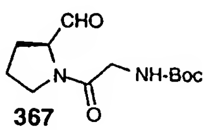
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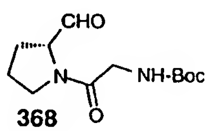
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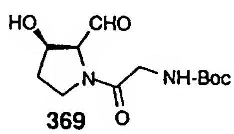
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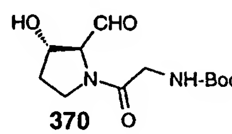
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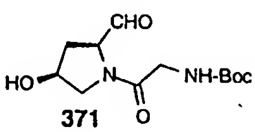
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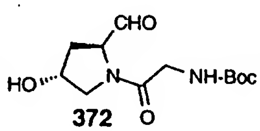
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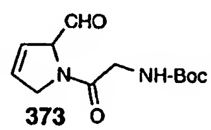
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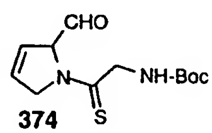
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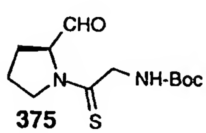
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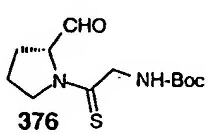
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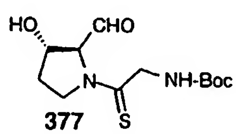
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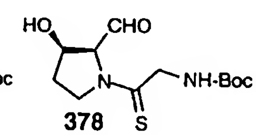
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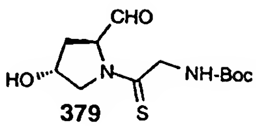
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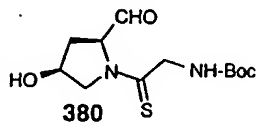
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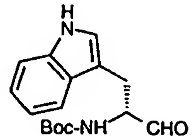
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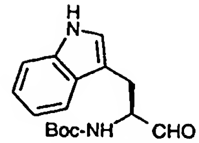
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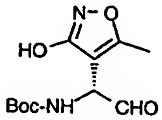
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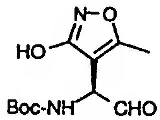
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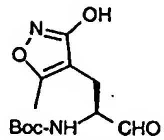
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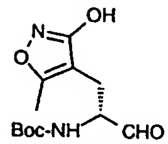
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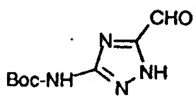
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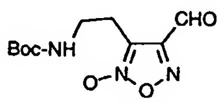
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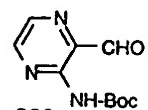
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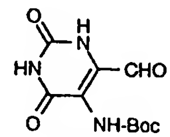
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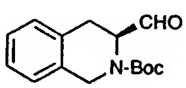
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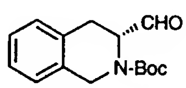
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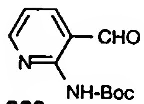
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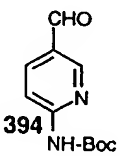
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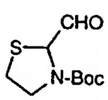
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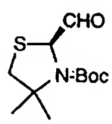
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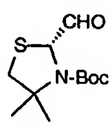
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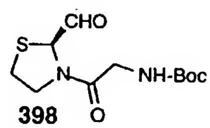
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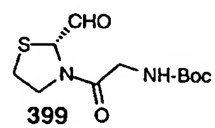
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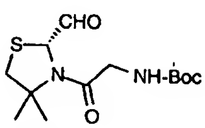
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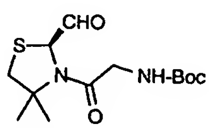
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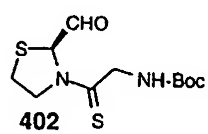
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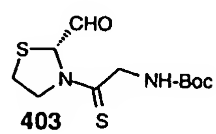
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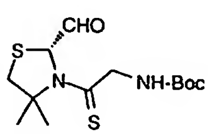
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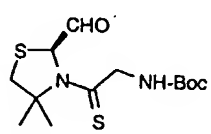
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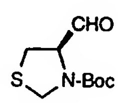
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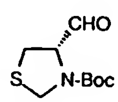
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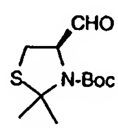
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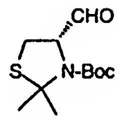
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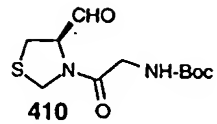
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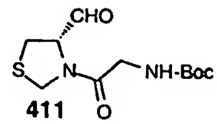
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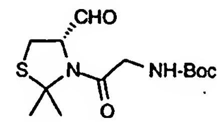
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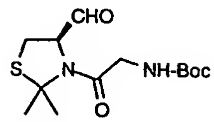
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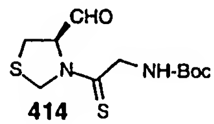
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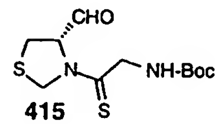
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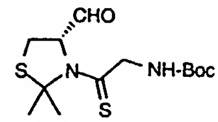
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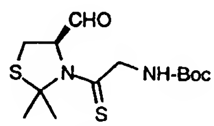
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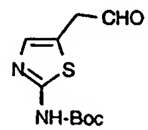
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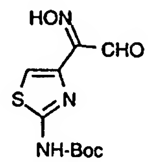
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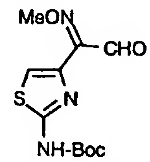
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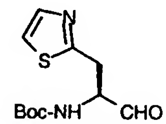
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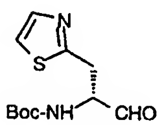
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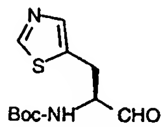
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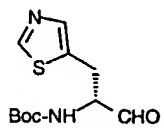
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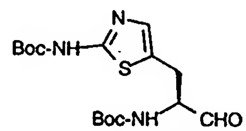
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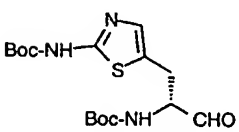
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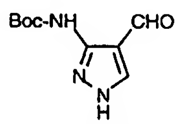
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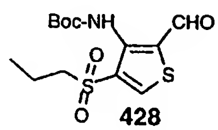
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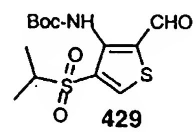
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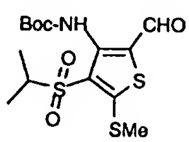
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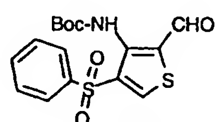
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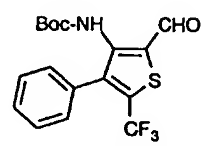
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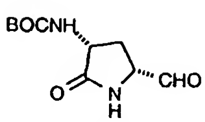
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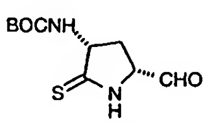
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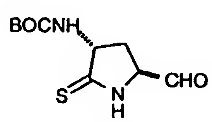
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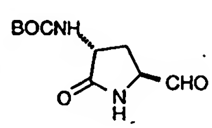
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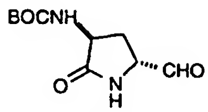

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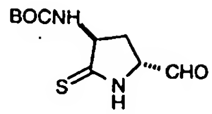

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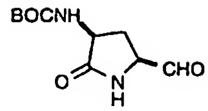

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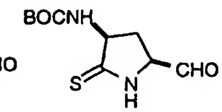

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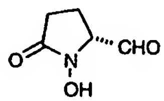

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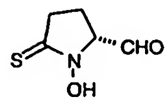

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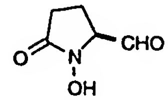

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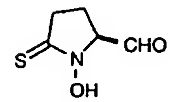

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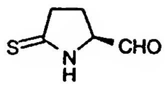

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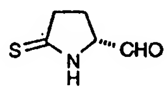

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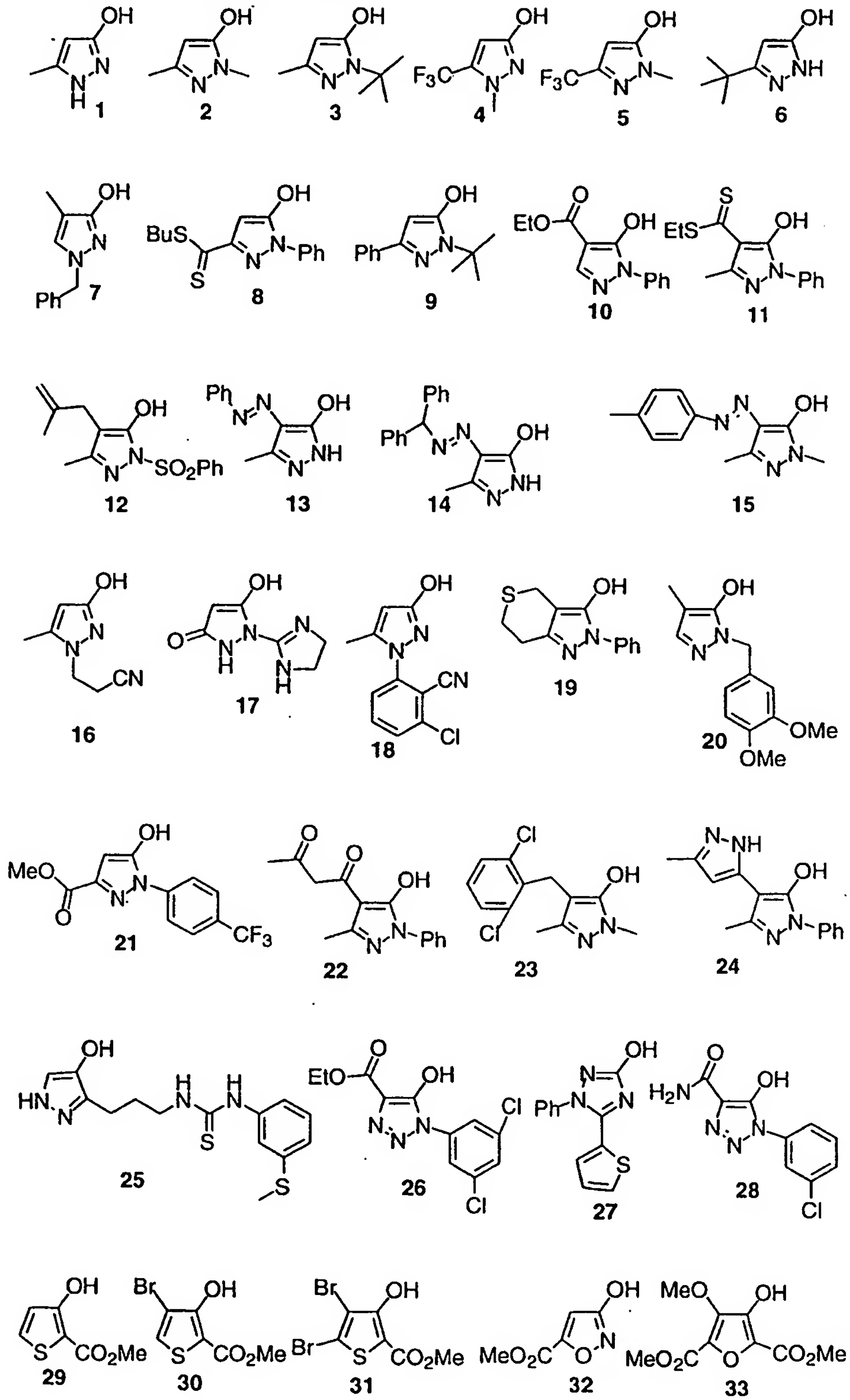
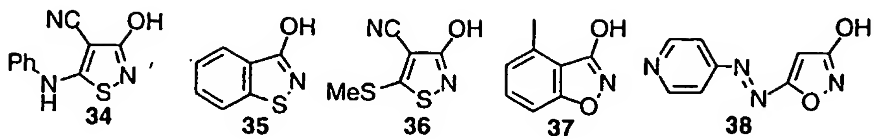
Table 15. Alcohols of the type A-OH





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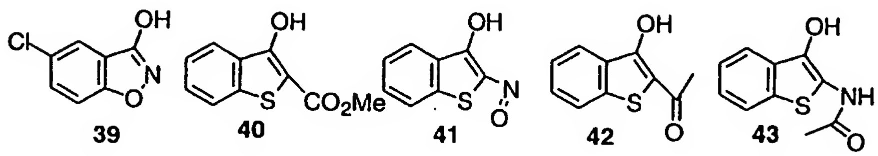

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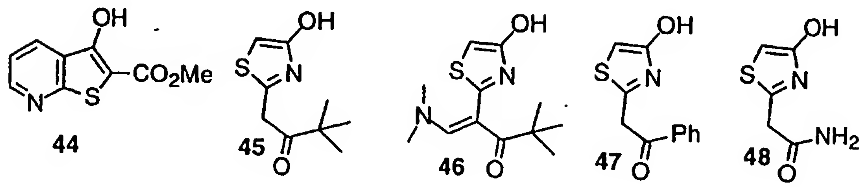

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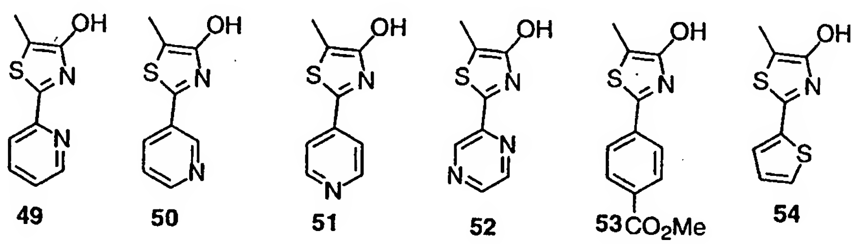

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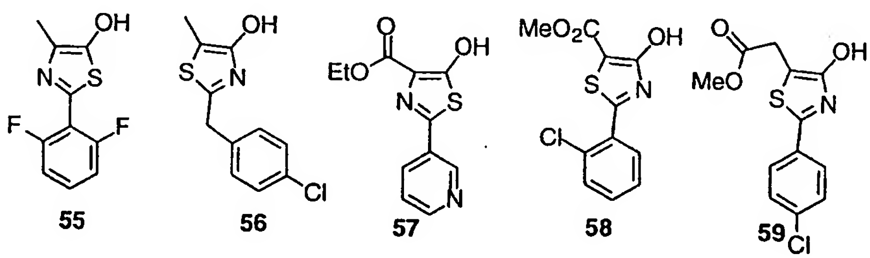

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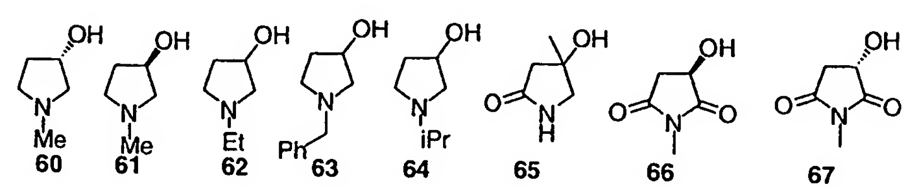

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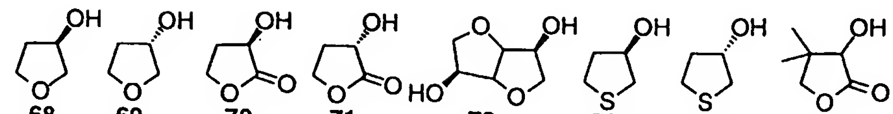

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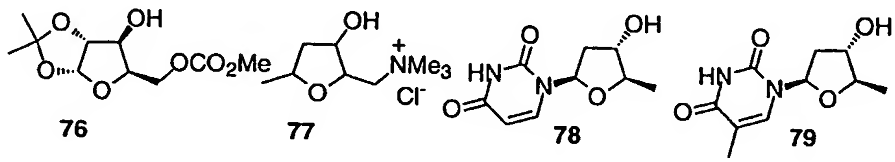

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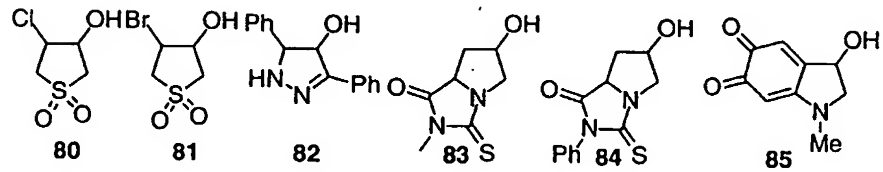

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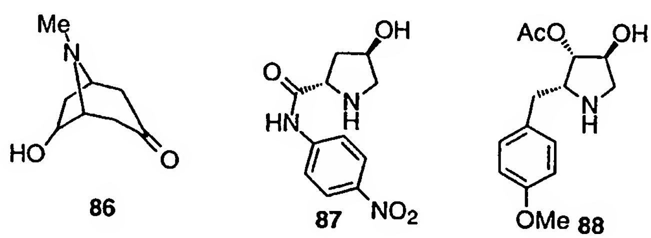

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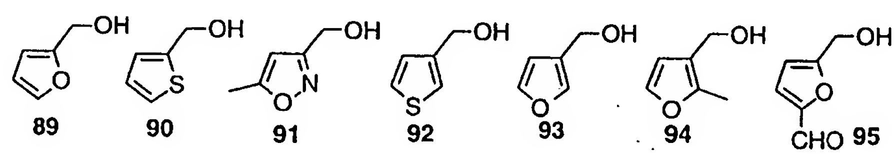

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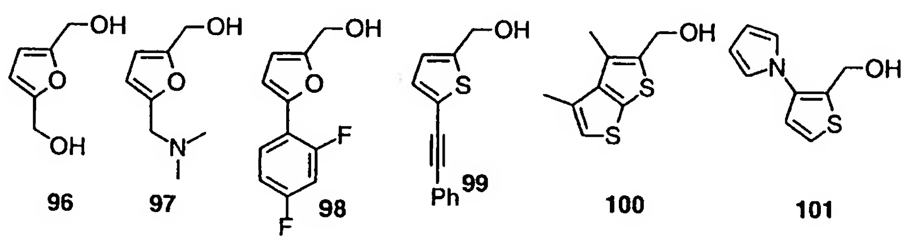

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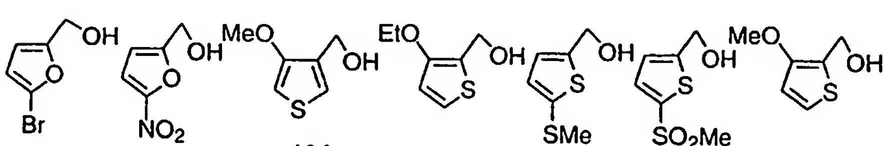

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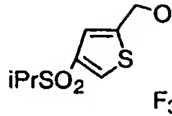
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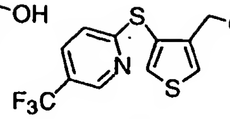
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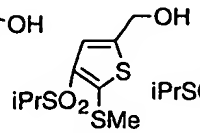
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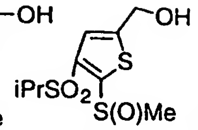
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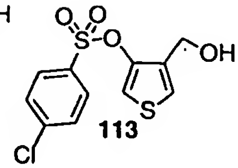
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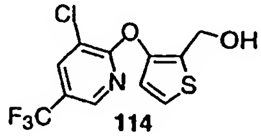
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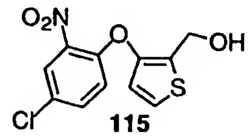
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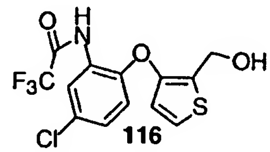
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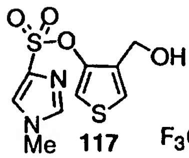
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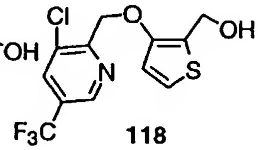
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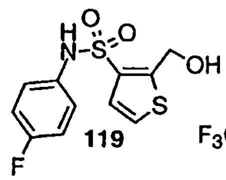
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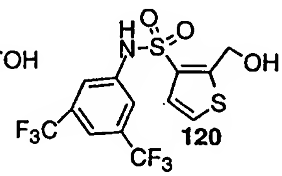
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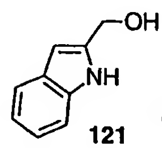
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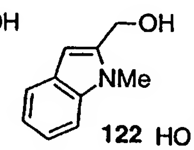
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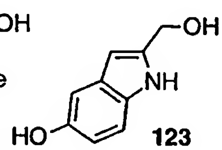
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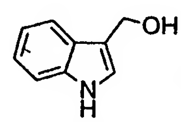
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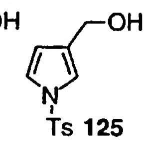
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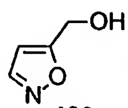
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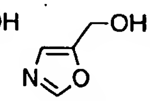
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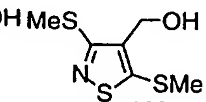
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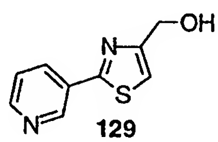
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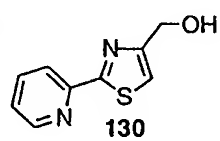
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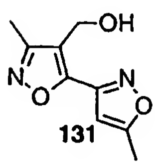
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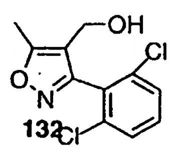
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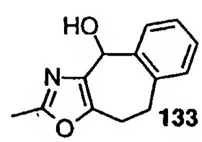
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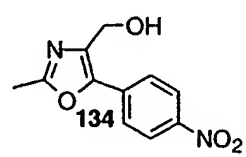
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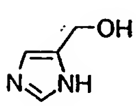
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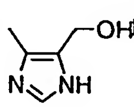
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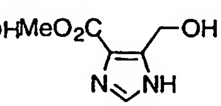
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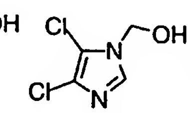
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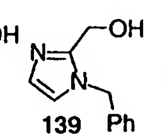
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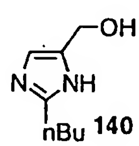
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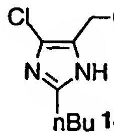
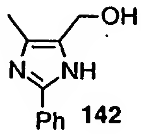
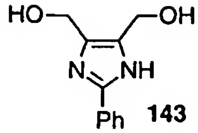
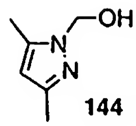
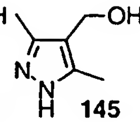
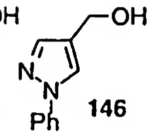
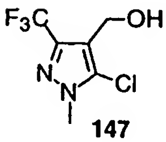
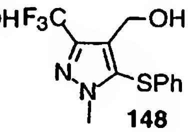
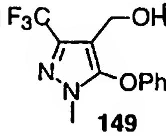
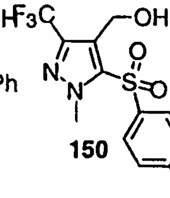
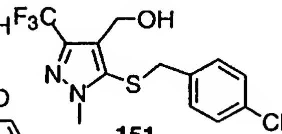
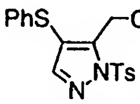
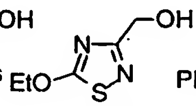
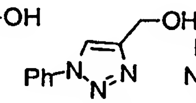
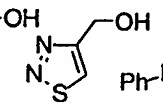
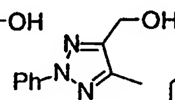
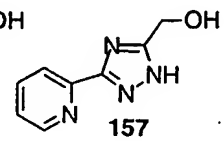
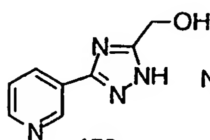
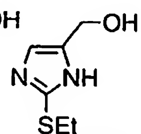
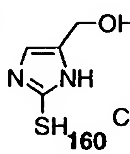
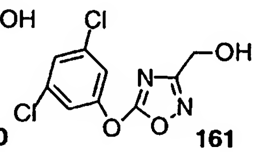
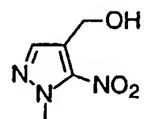
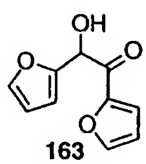
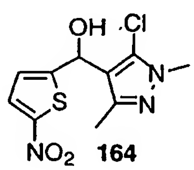
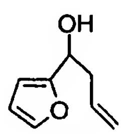
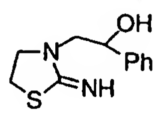
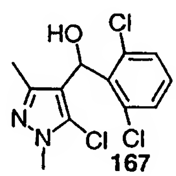
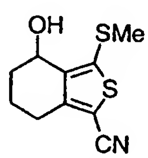
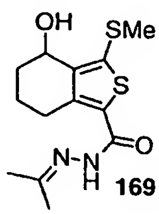
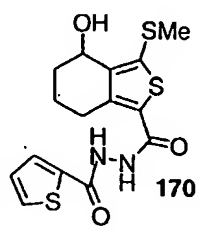
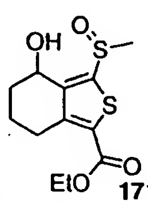
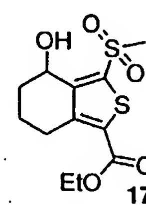
 141  142  143  144  145  146

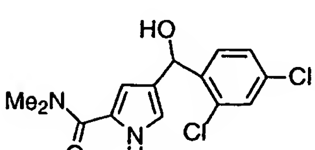
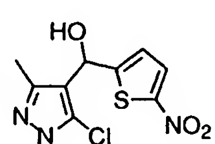
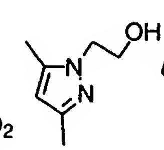
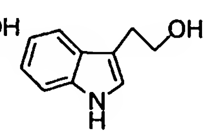
 147  148  149  150  151

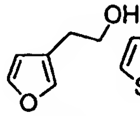
 152  153  154  155  156  157

 158  159  160  161  162

 163  164  165  166  167

 168  169  170  171  172

 173  174  175  176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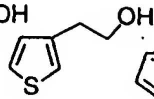
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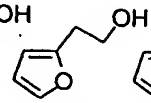
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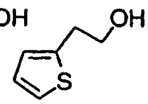
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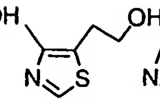
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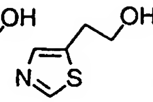
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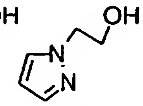
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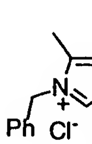
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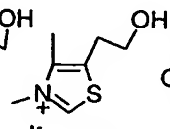
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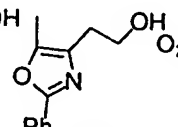
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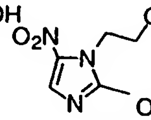
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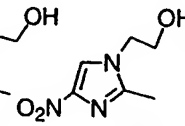
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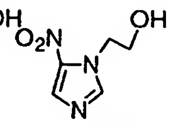
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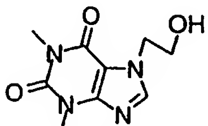
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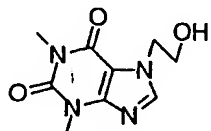
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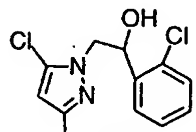
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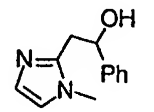
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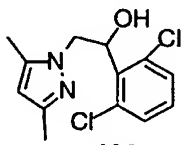
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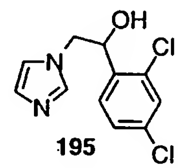
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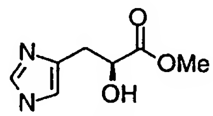
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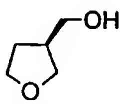
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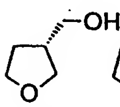
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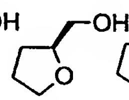
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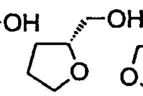
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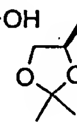
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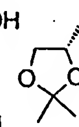
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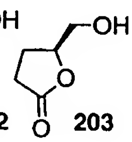
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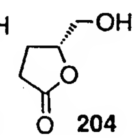
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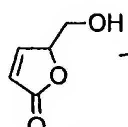
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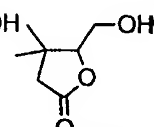
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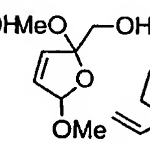
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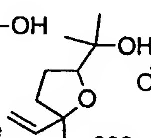
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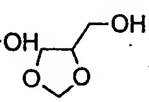
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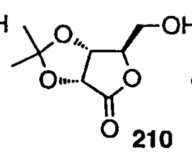
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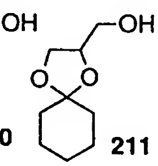
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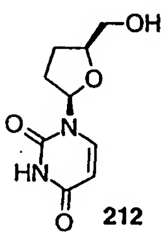
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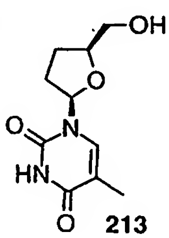
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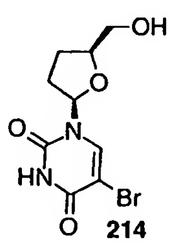
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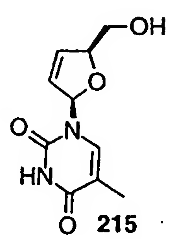
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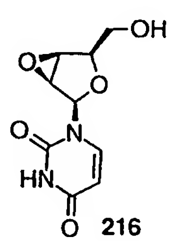
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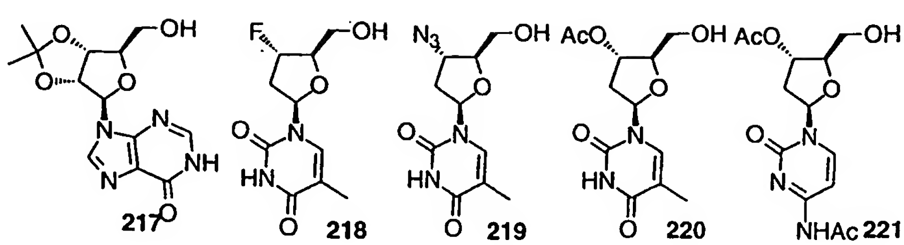

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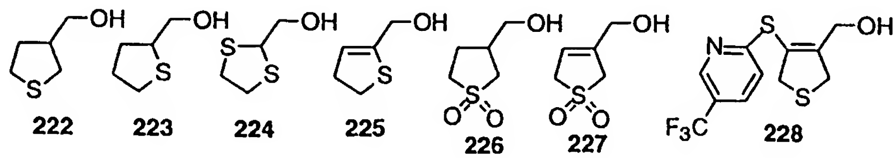

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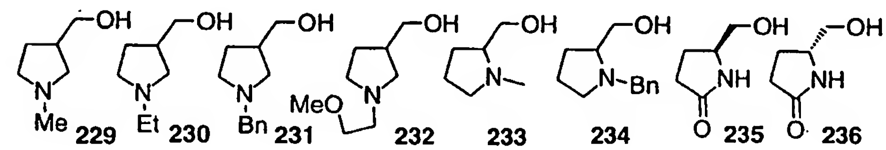

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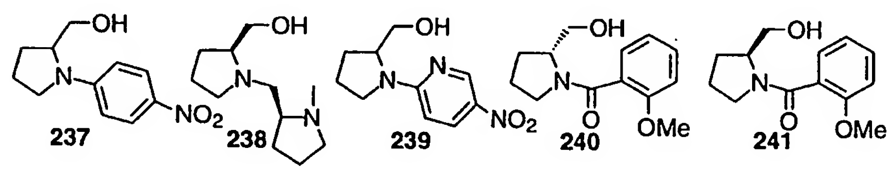

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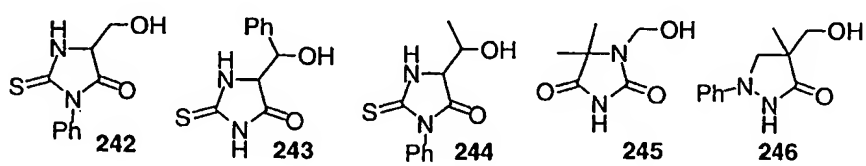

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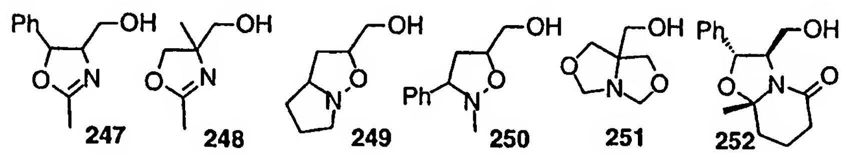

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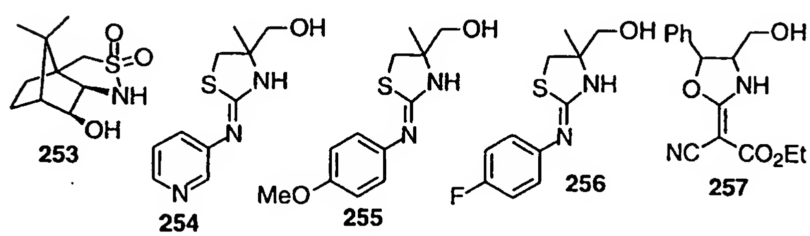

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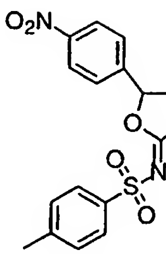
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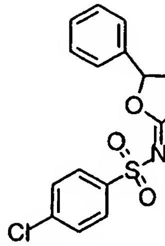
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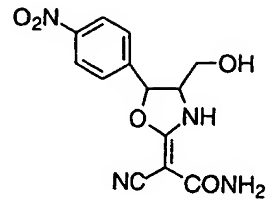
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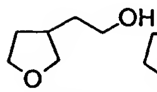
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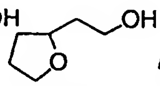
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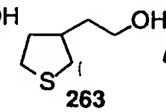
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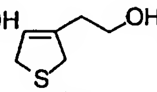
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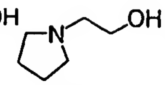
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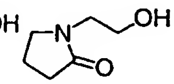
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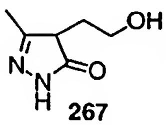
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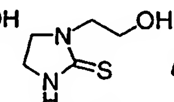
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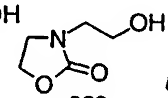
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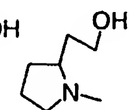
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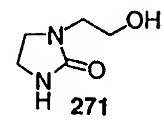
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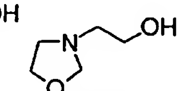
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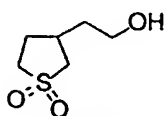
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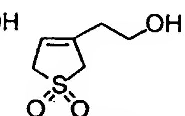
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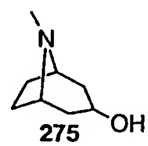
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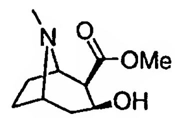
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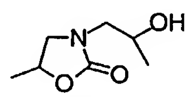
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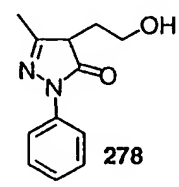
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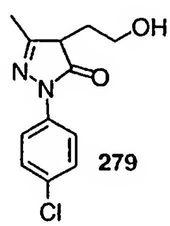
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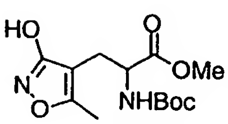
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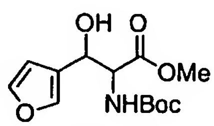
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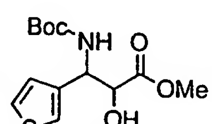
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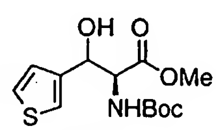
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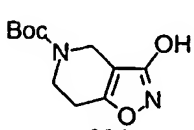
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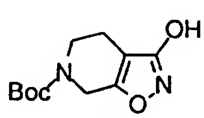
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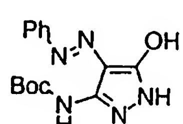
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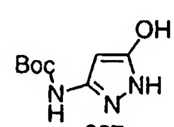
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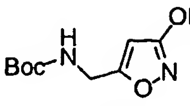
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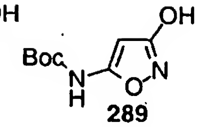
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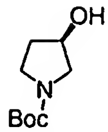
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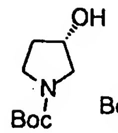
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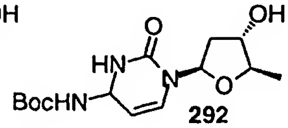
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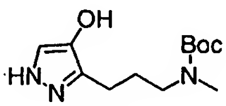
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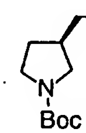
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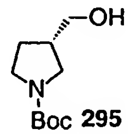
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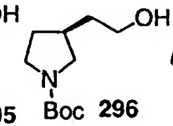
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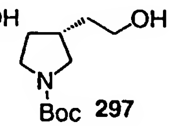
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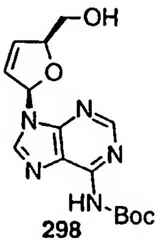
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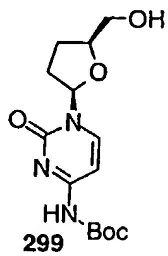
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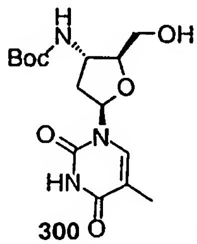
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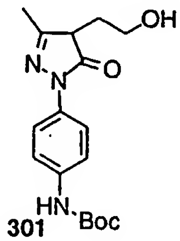
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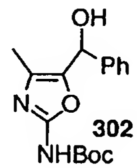
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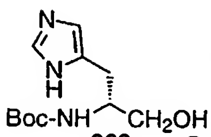
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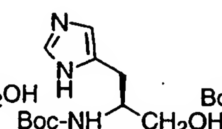
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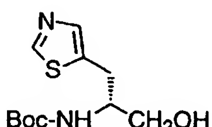
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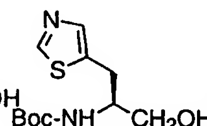
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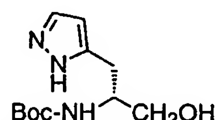
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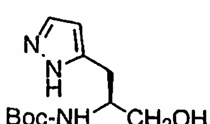
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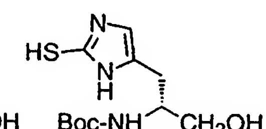
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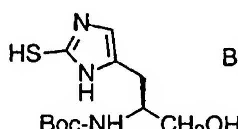
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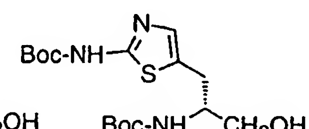
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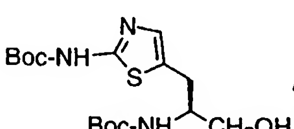
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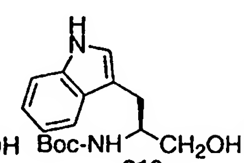
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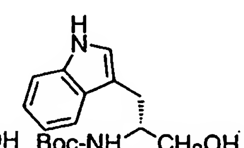
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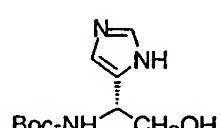
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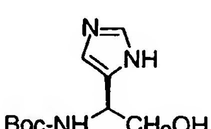
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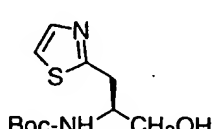
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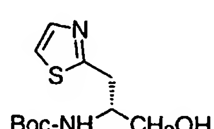
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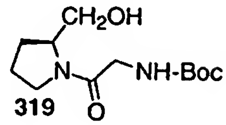
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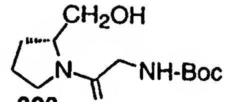
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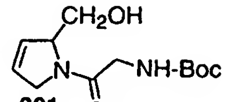
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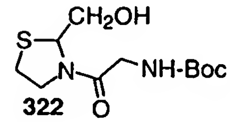
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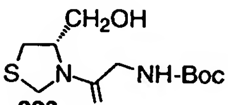
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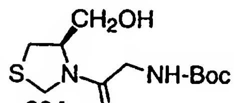
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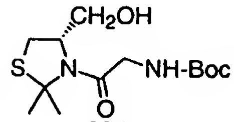
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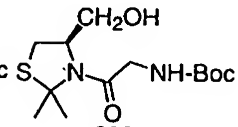
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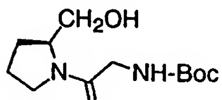
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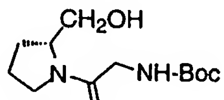
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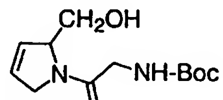
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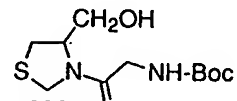
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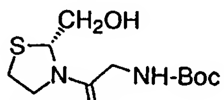
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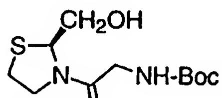
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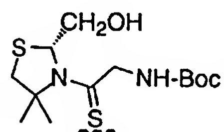
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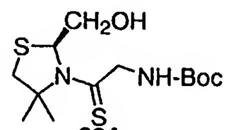
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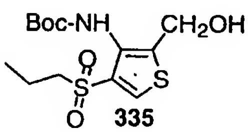
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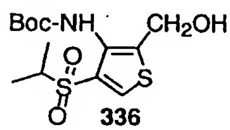
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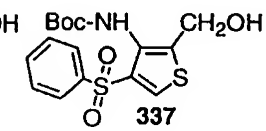
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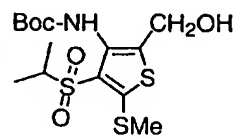
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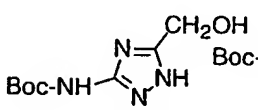
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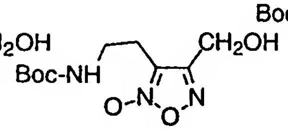
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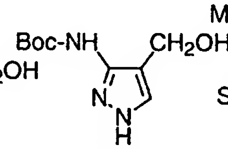
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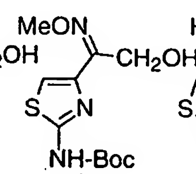
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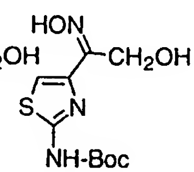
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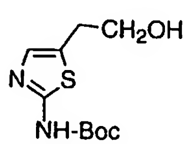
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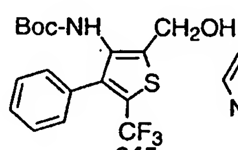
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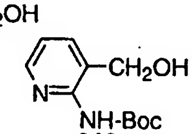
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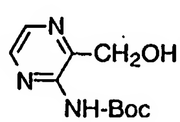
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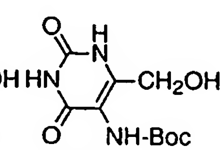
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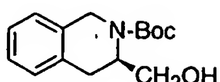
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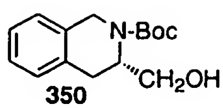
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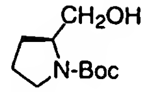
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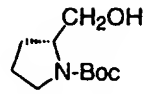
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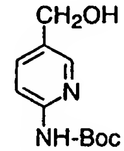
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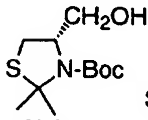
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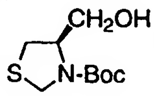
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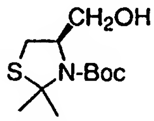
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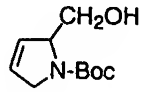
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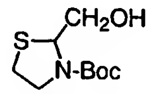
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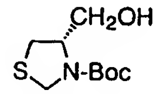
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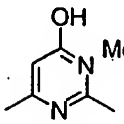
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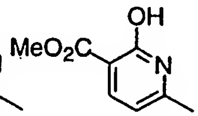
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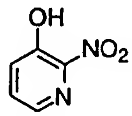
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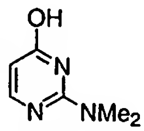
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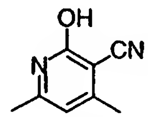
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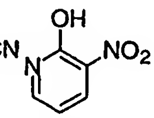
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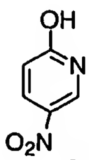
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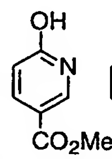
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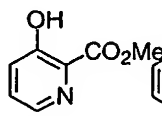
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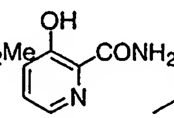
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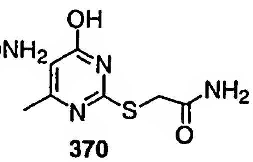
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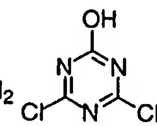
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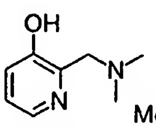
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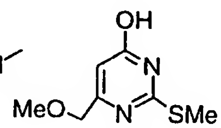
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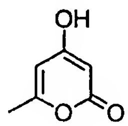
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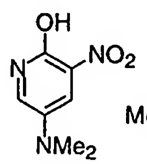
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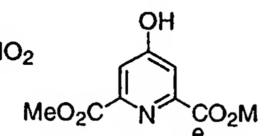
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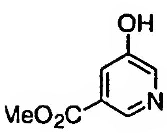
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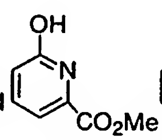
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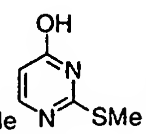
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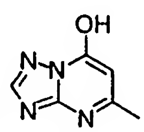
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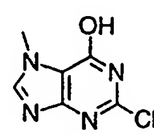
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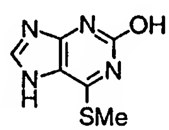
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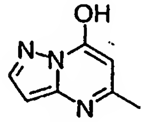
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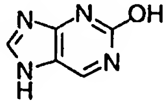
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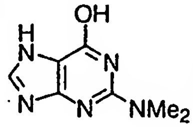
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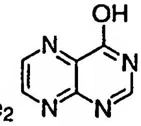
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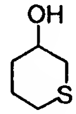
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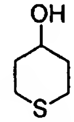
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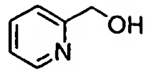
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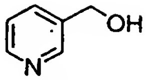
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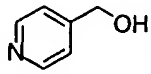
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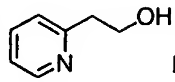
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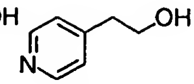
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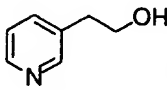
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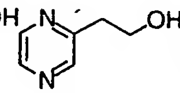
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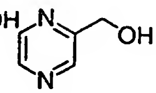
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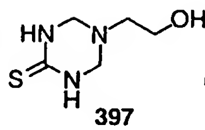
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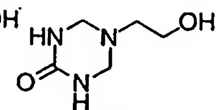
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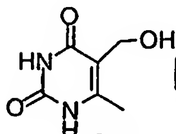
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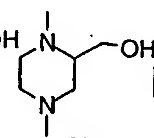
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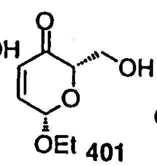
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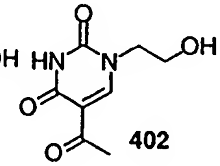
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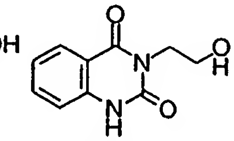
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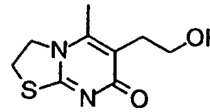
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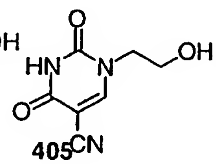
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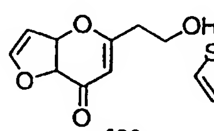
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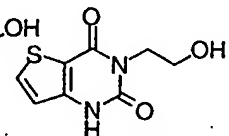
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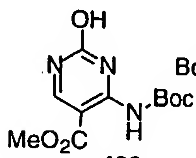
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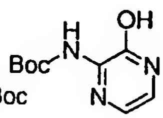
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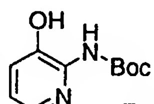
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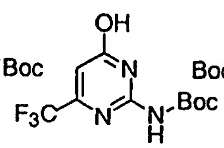
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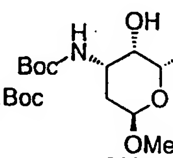
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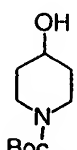
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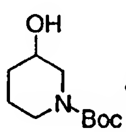
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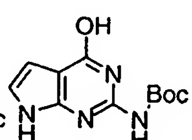
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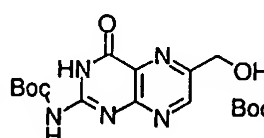
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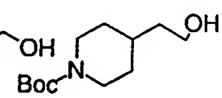
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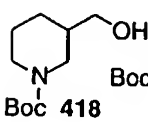
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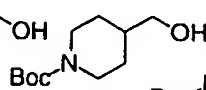
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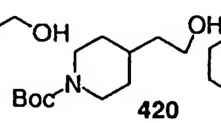
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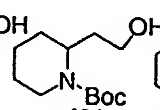
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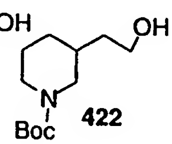
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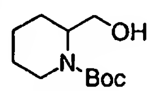
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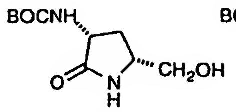

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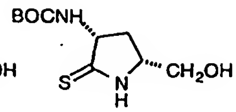

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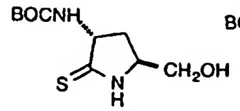

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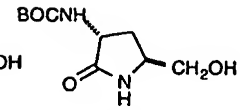

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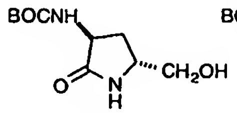

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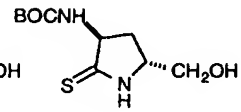

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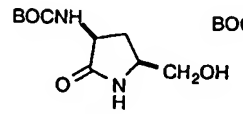

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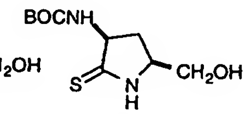

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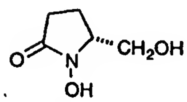

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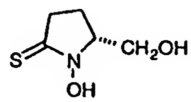

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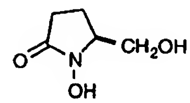

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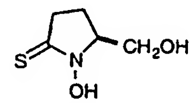

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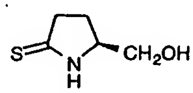

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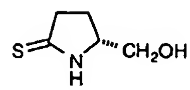

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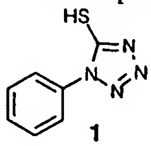
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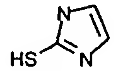
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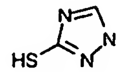
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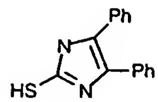
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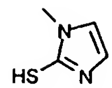
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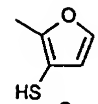
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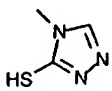
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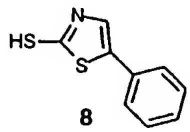
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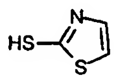
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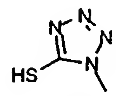
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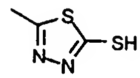
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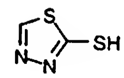
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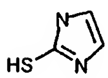
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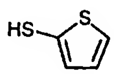
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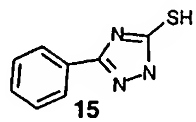
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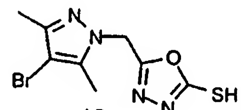
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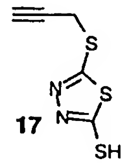
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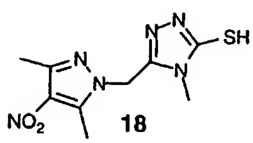
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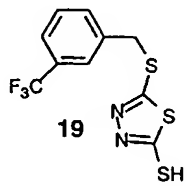
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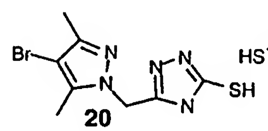
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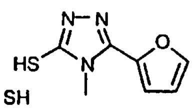
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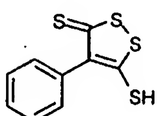
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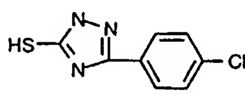
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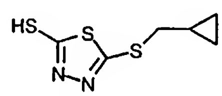
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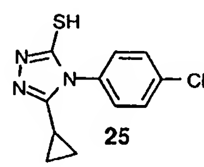
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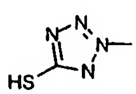
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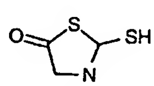
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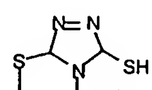
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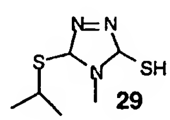
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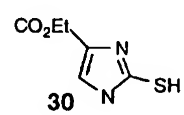
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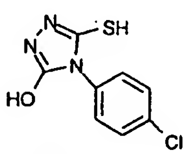
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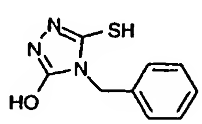
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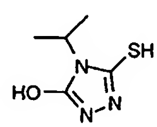
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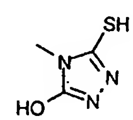
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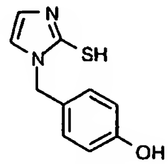
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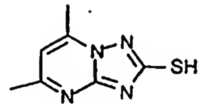
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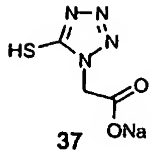
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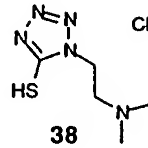
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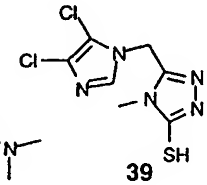
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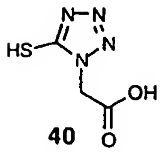
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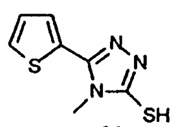
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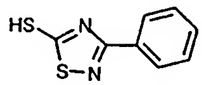
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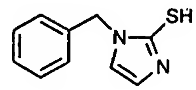
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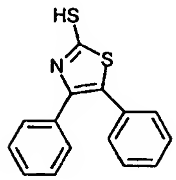
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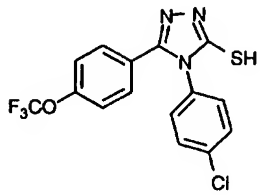
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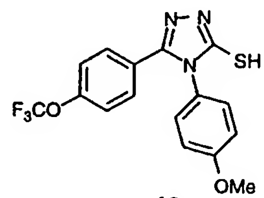
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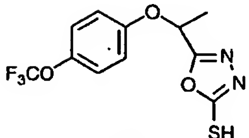
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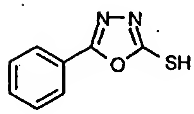
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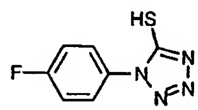
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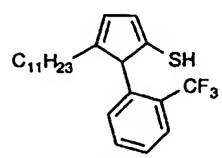
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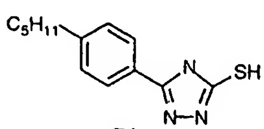
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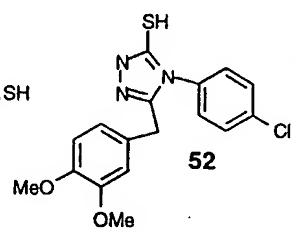
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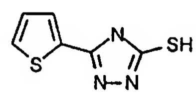
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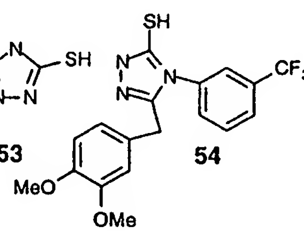
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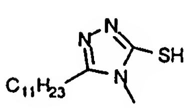
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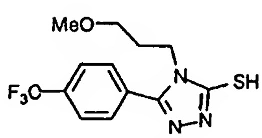
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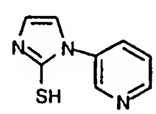
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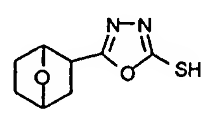
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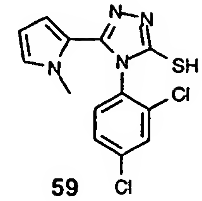
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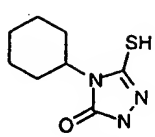
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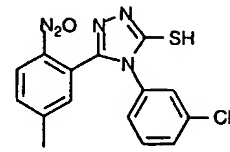
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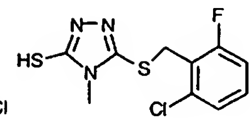
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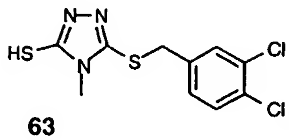
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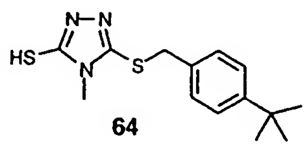
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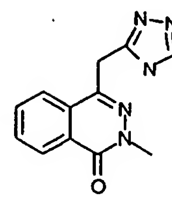
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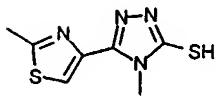
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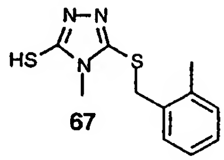
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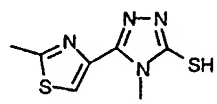
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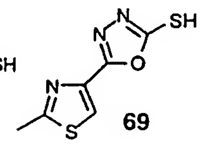
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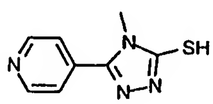
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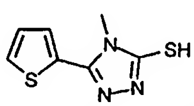
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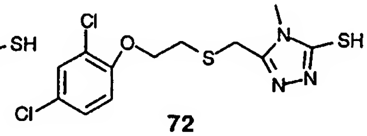
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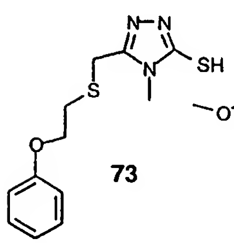
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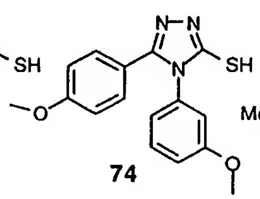
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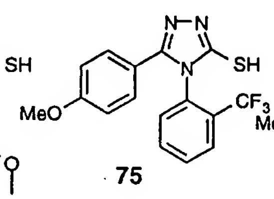
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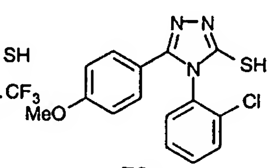
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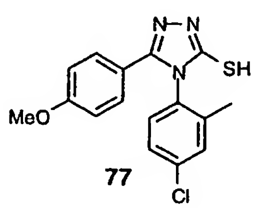
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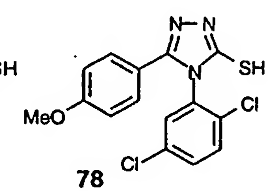
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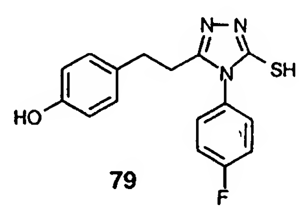
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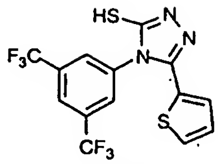
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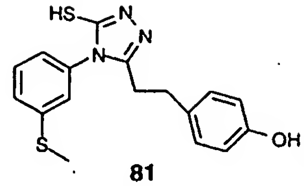
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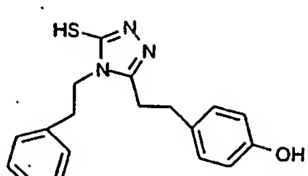
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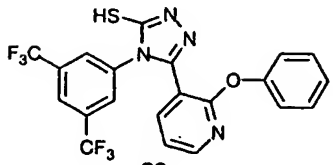
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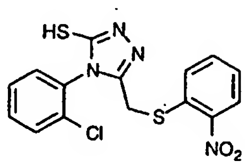
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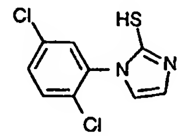
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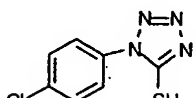
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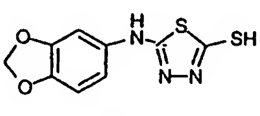
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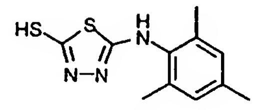
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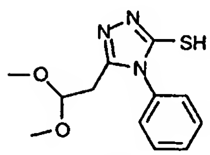
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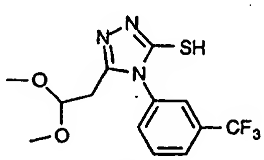
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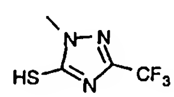
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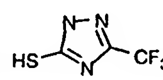
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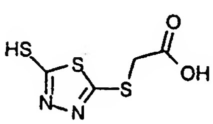
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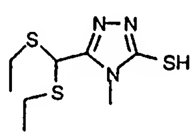
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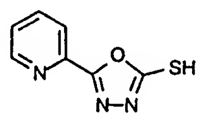
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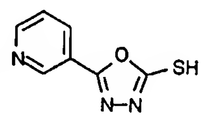
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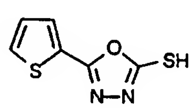
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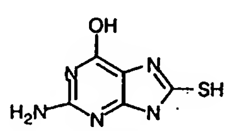
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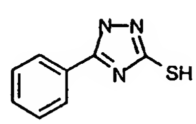
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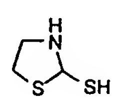
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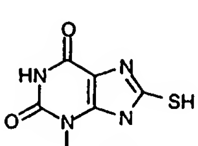
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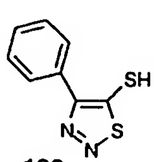
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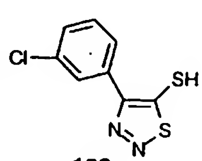
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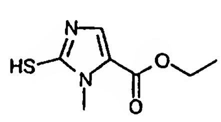
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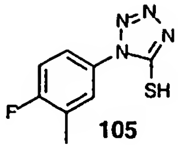
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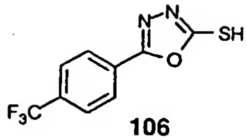
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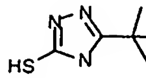
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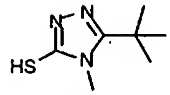
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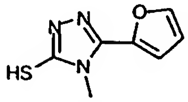
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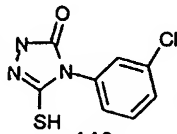
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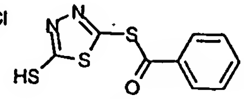
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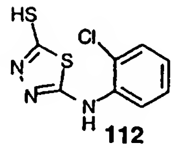
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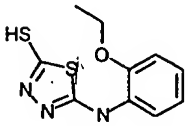
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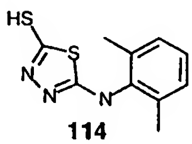
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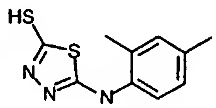
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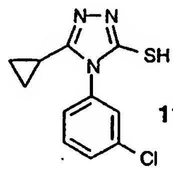
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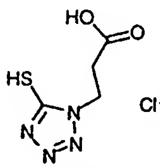
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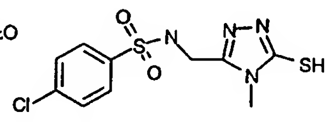
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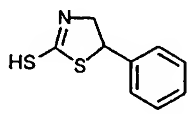
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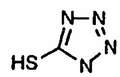
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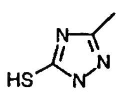
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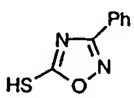
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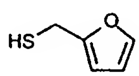
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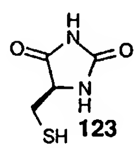
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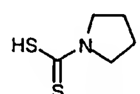
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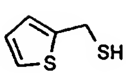
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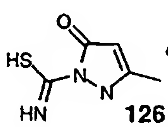
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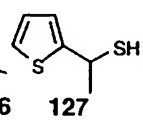
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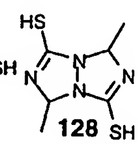
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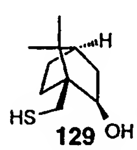
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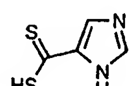
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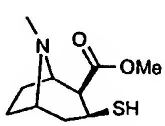
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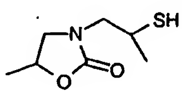
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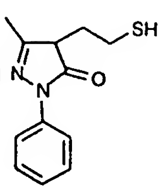
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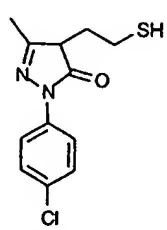
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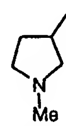
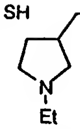
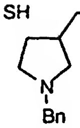
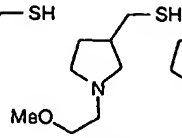
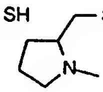
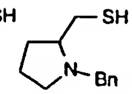
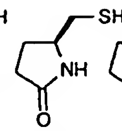
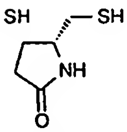
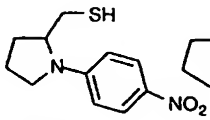
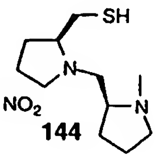
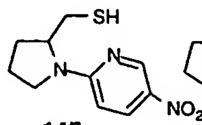
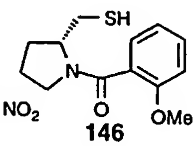
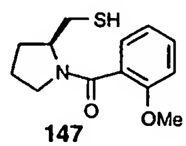
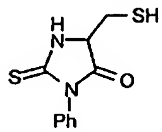
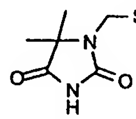
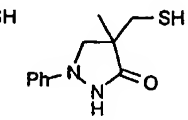
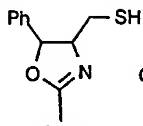
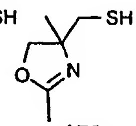
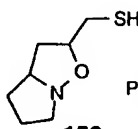
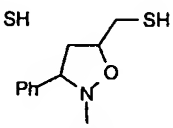
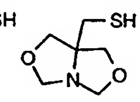
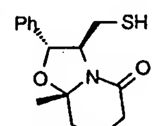
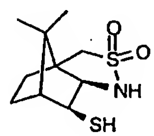
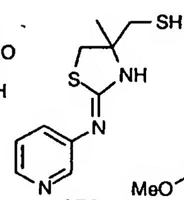
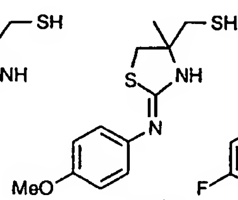
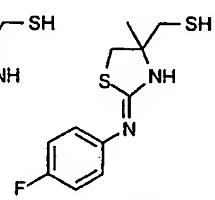
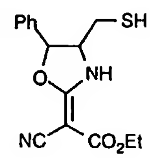
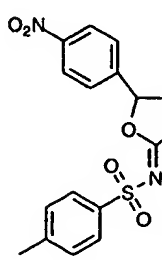
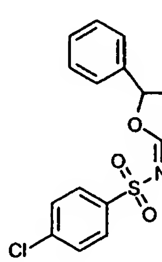
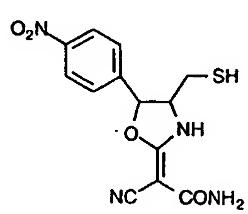
 135
 136
 137
 138
 139
 140
 141
 142

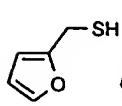
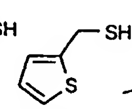
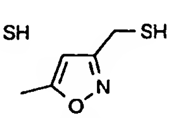
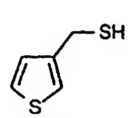
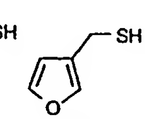
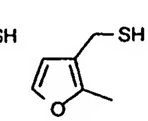
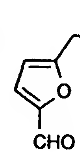
 143
 144
 145
 146
 147

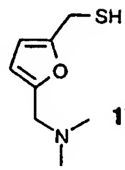
 148
 149
 150

 151
 152
 153
 154
 155
 156

 157
 158
 159
 160
 161

 162
 163
 164

 165
 166
 167
 168
 169
 170
 171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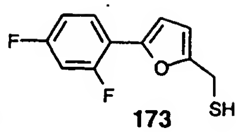
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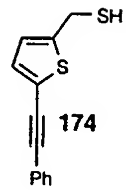
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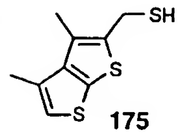
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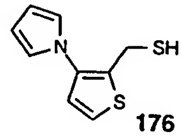
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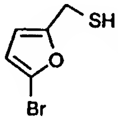
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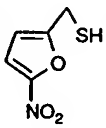
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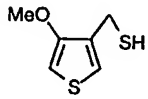
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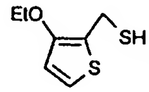
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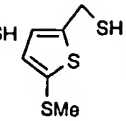
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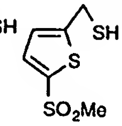
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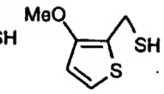
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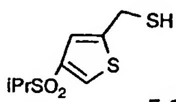
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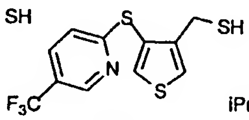
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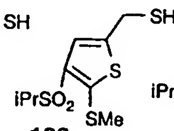
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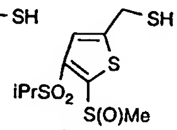
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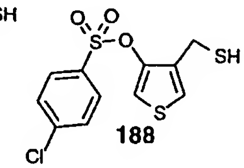
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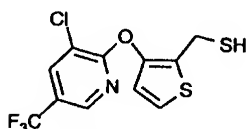
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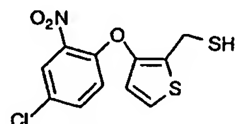
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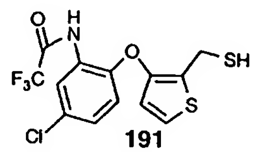
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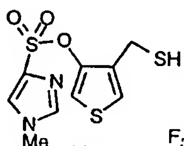
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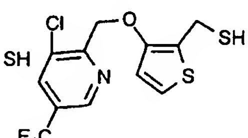
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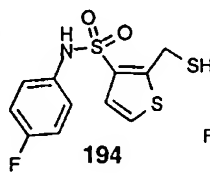
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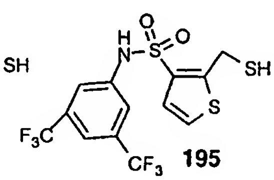
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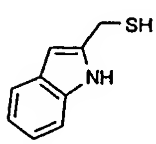
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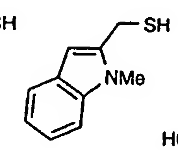
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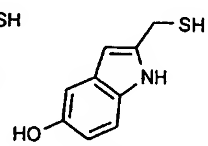
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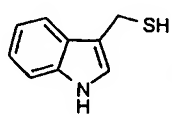
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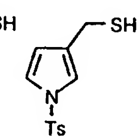
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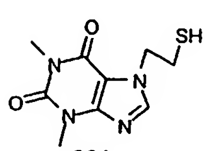
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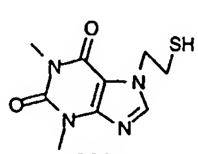
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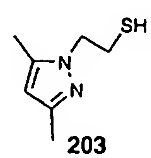
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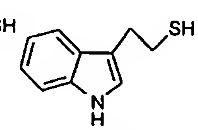
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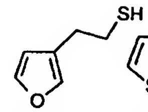
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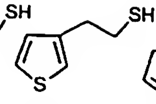
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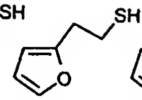
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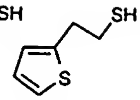
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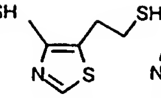
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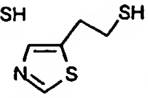
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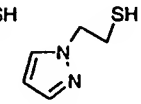
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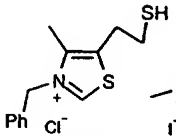
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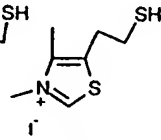
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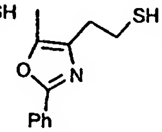
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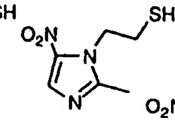
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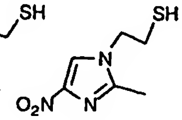
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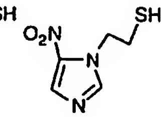
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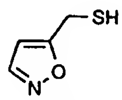
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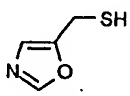
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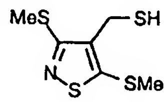
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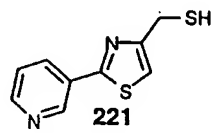
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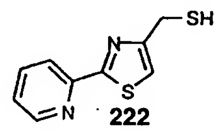
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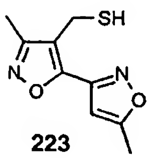
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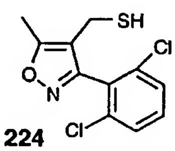
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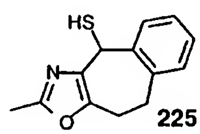
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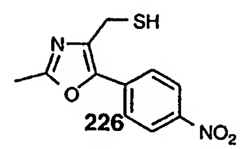
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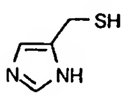
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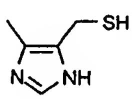
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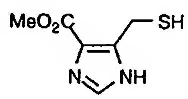
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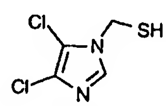
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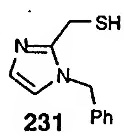
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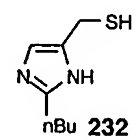
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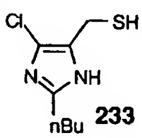
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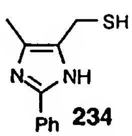
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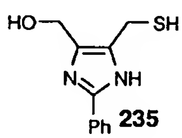
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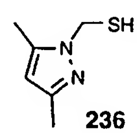
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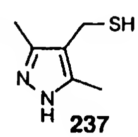
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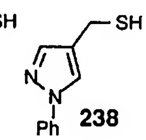
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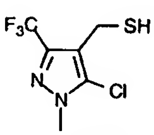
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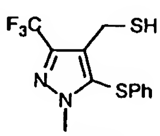
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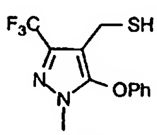
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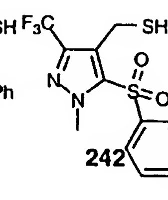
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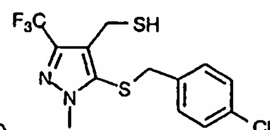
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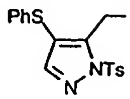
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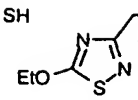
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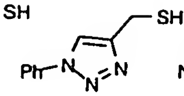
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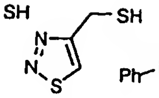
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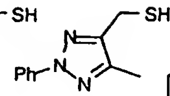
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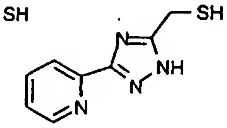
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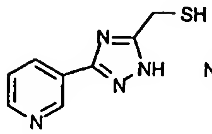
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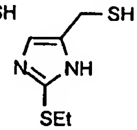
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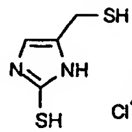
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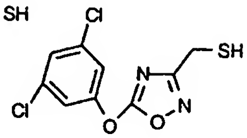
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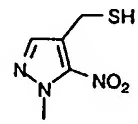
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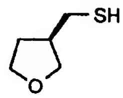
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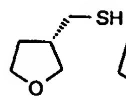
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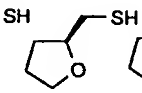
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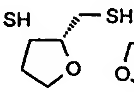
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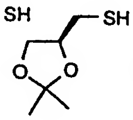
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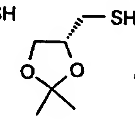
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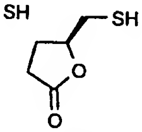
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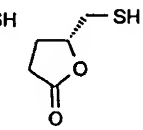
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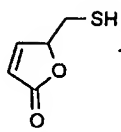
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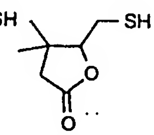
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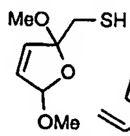
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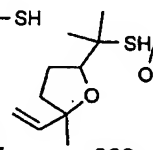
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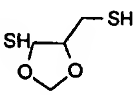
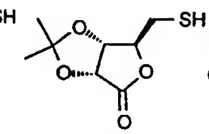
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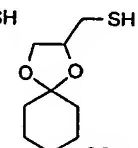
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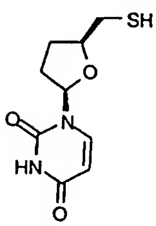
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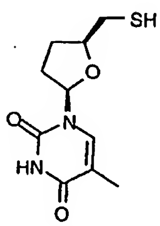
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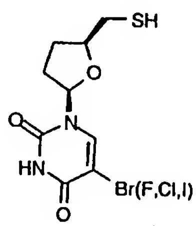
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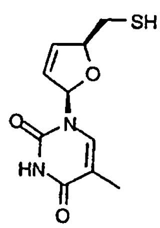
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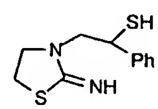
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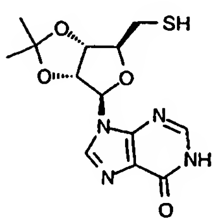
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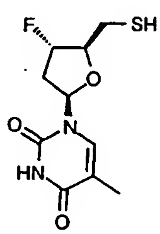
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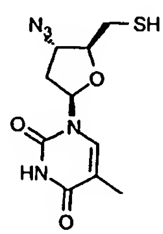
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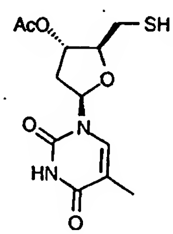
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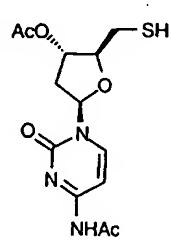
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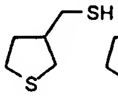 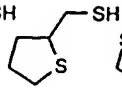 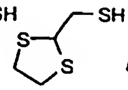 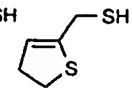 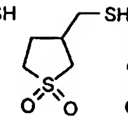 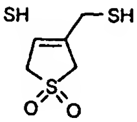 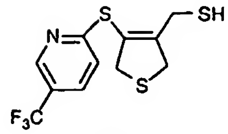

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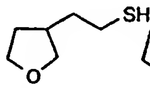 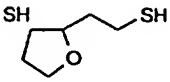 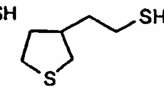 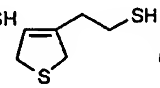 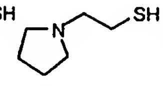 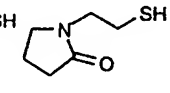

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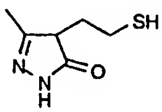 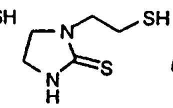 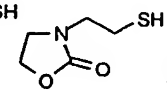 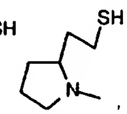 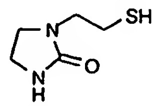 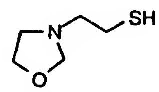

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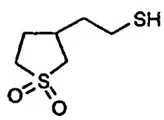 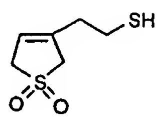 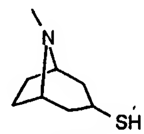

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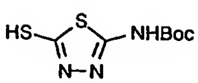 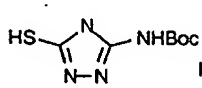 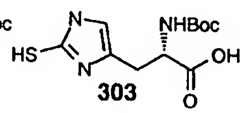 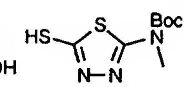

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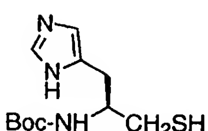 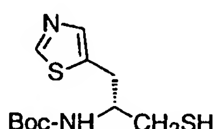 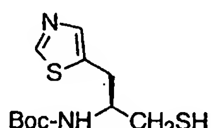 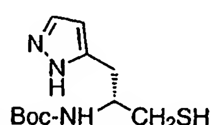

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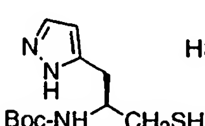 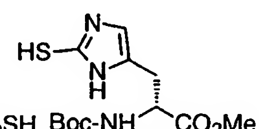 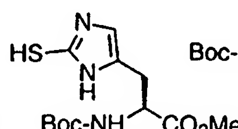 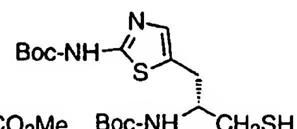

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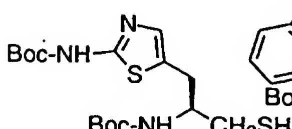 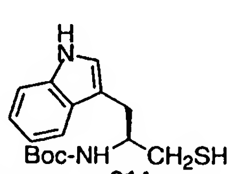 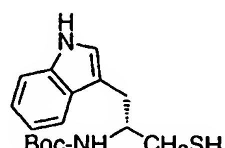 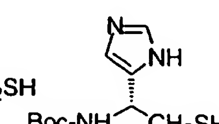

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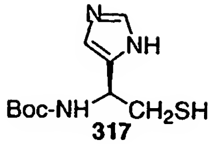
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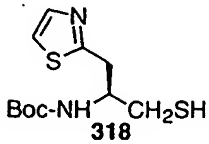
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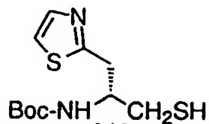
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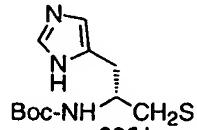
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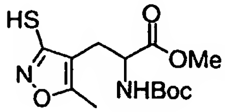
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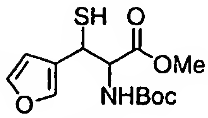
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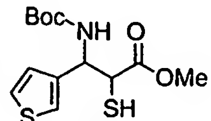
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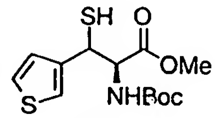
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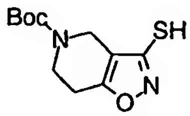
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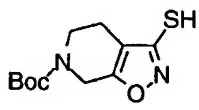
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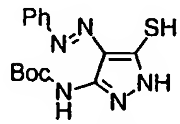
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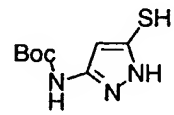
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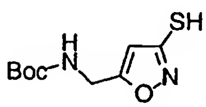
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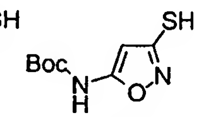
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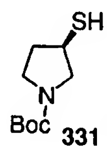
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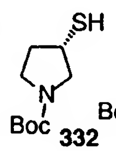
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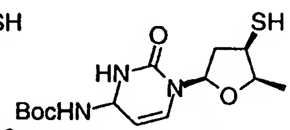
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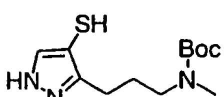
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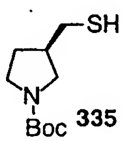
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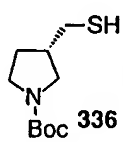
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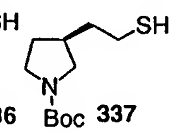
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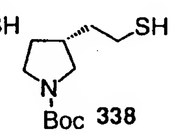
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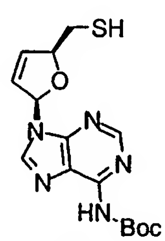
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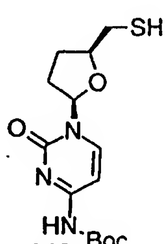
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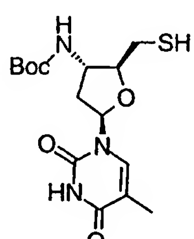
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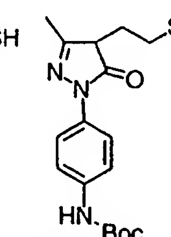
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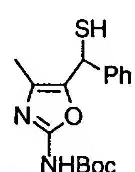
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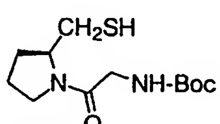
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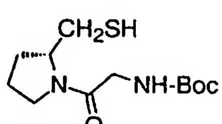
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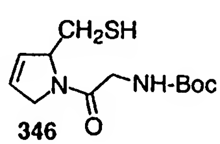
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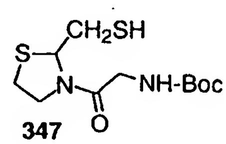
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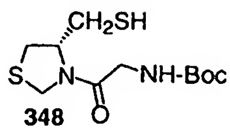
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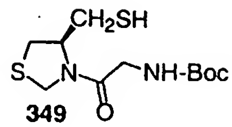
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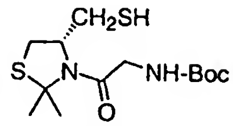
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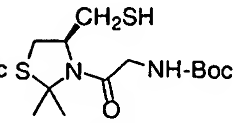
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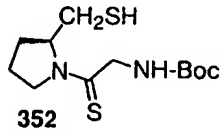
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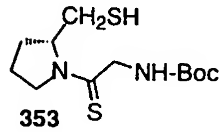
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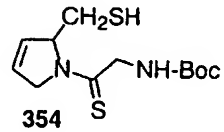
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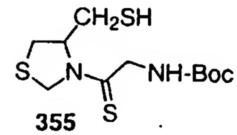
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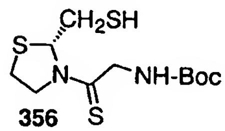
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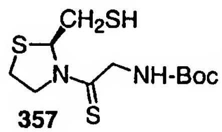
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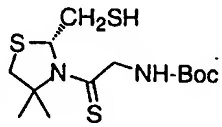
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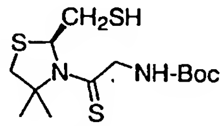
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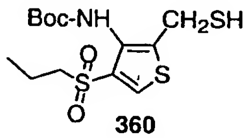
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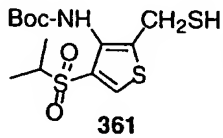
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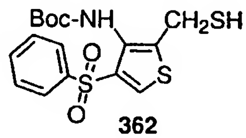
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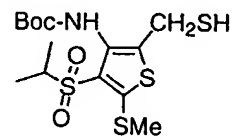
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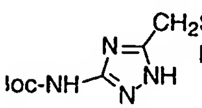
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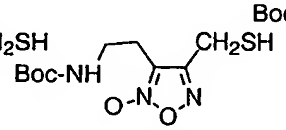
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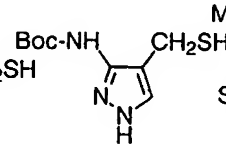
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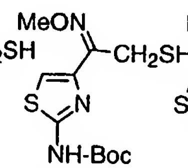
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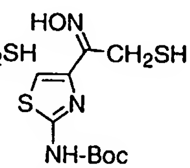
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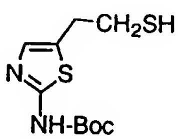
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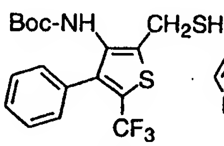
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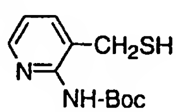
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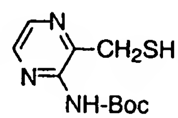
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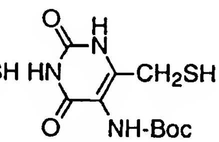
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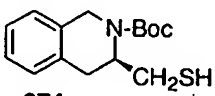
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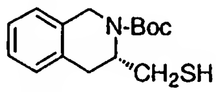
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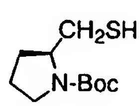
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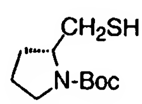
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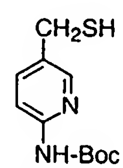
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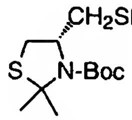
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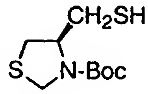
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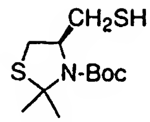
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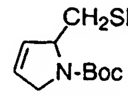
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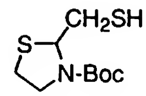
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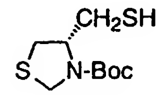
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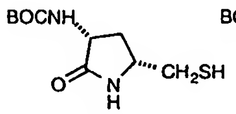
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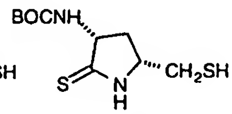
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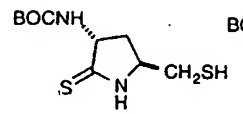
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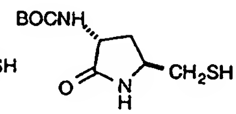
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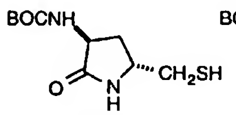
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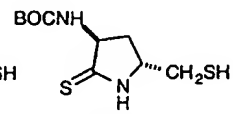
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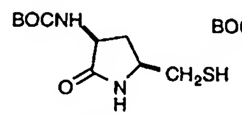
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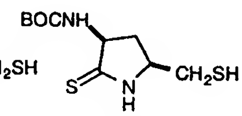
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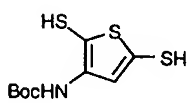
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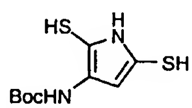
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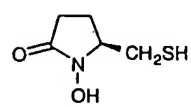
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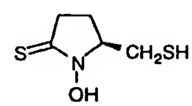
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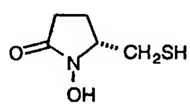
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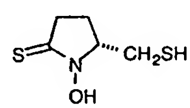
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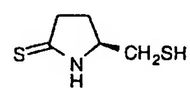
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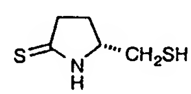
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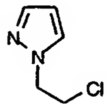
Table 17. Halides of the type A-Cl, A-Br, and A-I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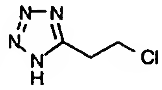
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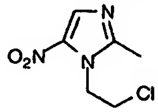
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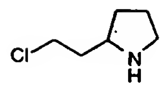
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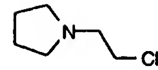
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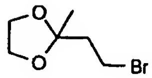
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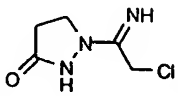
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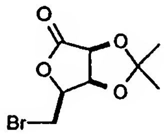
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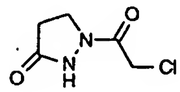
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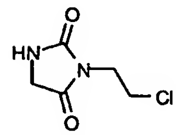
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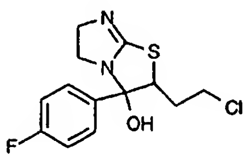
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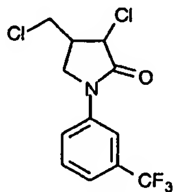
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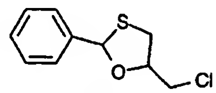
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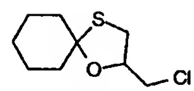
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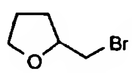
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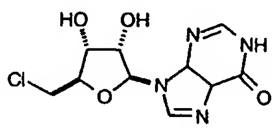
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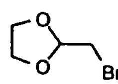
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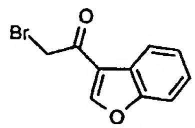
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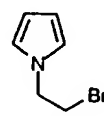
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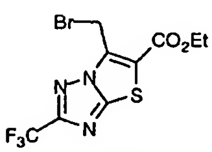
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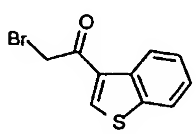
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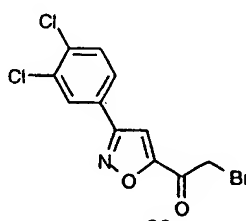
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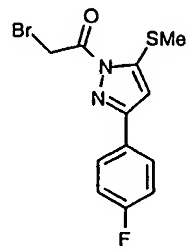
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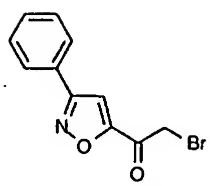
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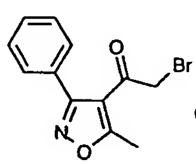
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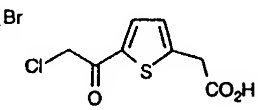
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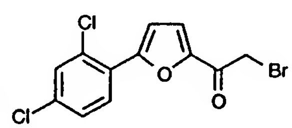
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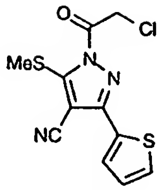
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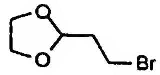
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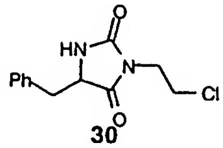
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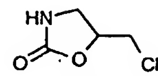
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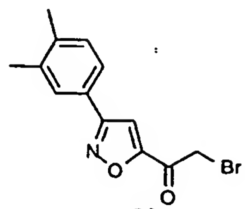
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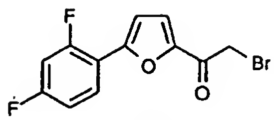
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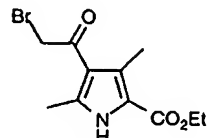
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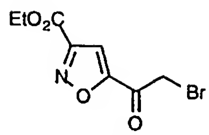
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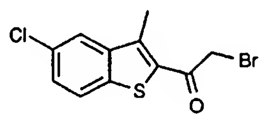
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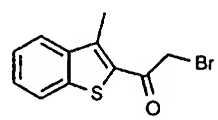
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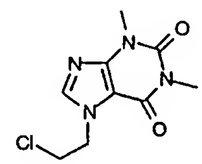
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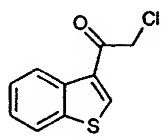
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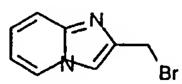
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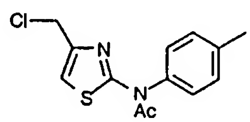
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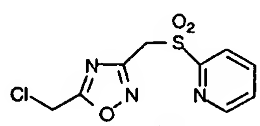
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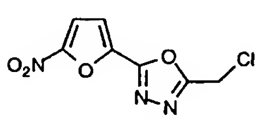
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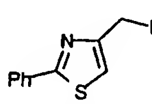
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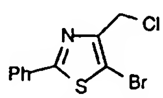
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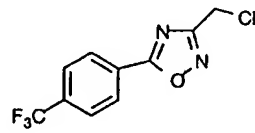
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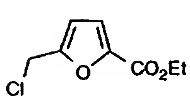
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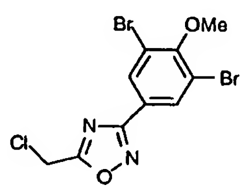
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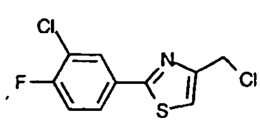
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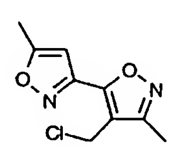
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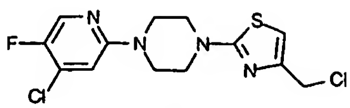
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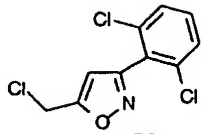
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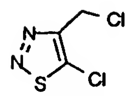
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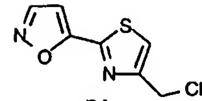
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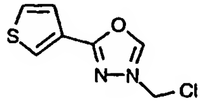
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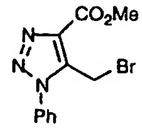
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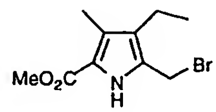
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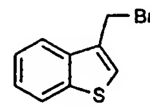
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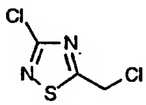
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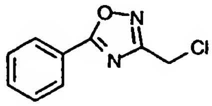
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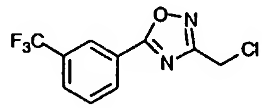
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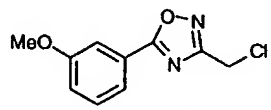
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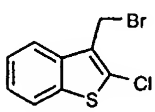
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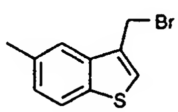
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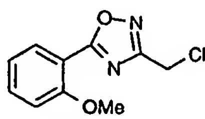
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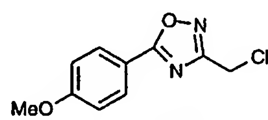
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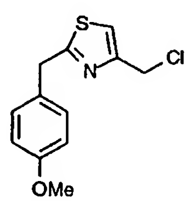
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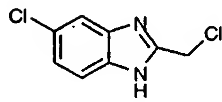
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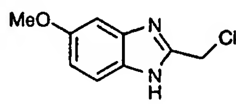
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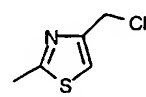
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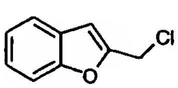
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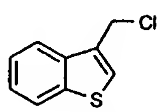
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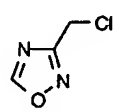
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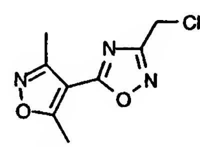
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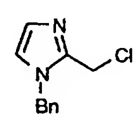
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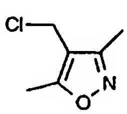
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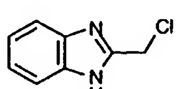
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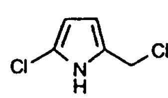
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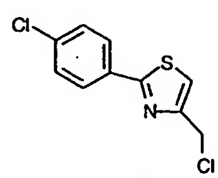
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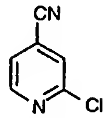
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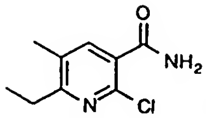
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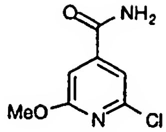
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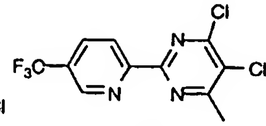
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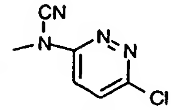
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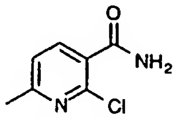
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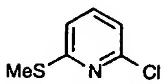
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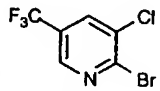
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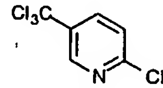
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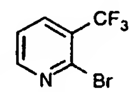
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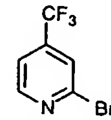
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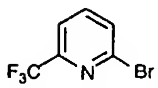
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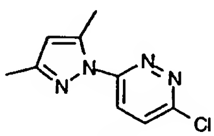
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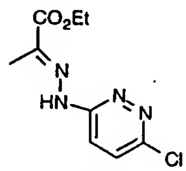
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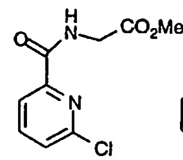
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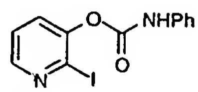
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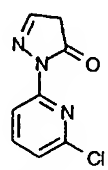
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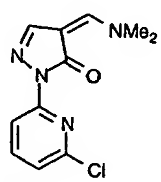
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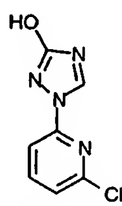
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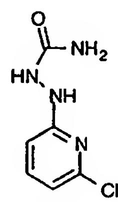
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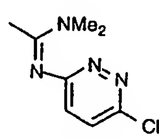
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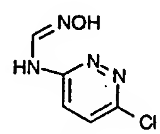
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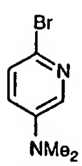
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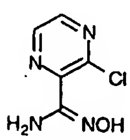
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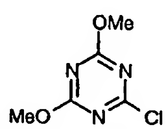
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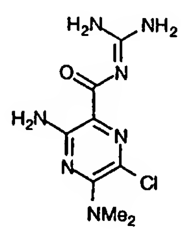
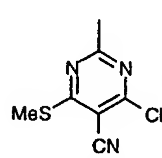
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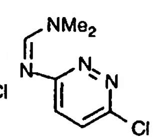
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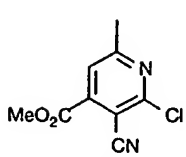
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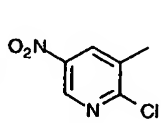
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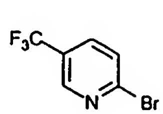
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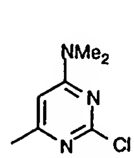
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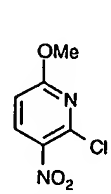
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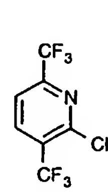
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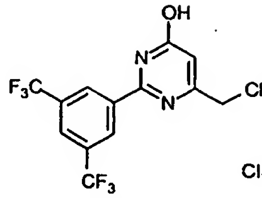

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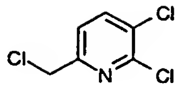

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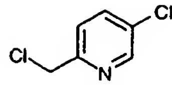

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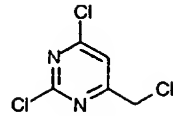

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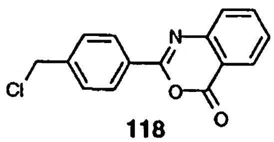

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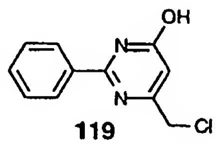

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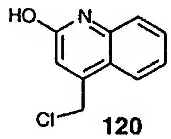

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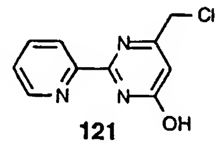

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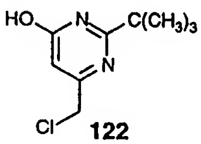

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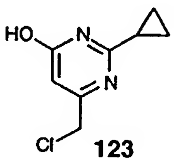

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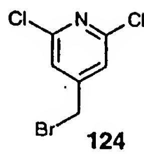

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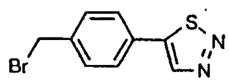

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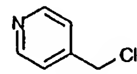

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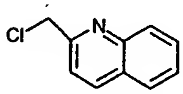

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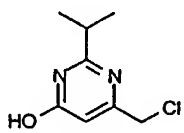

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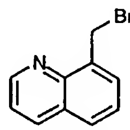

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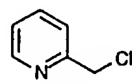

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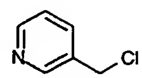

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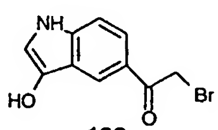

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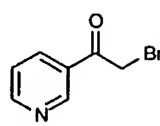

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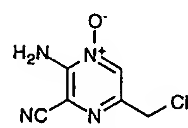

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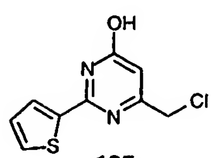

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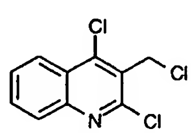

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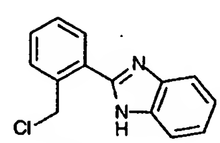

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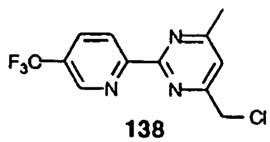
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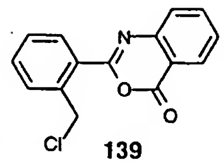
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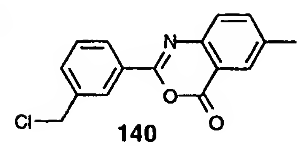
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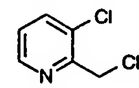
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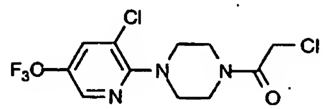
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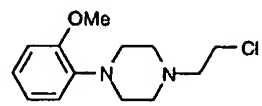
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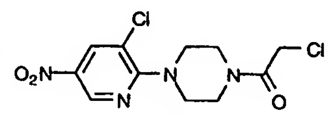
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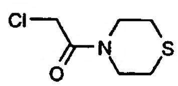
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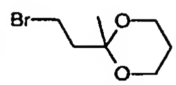
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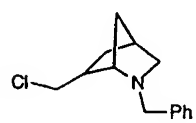
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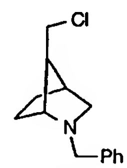
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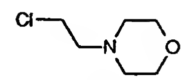
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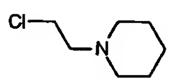
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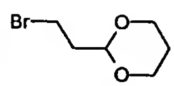
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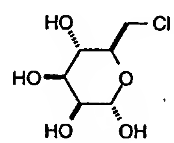
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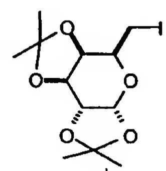
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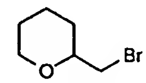
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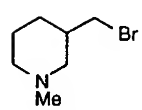
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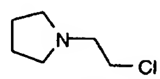
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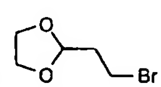
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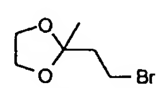
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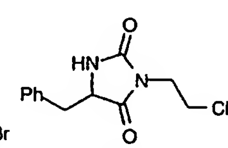
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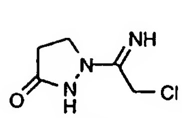
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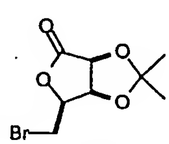
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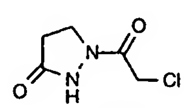
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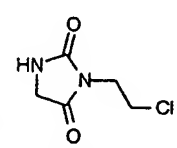
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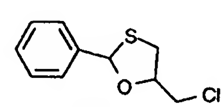
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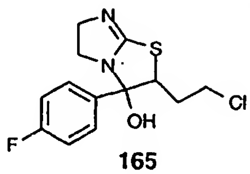
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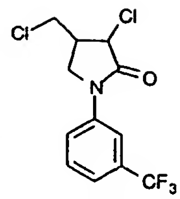
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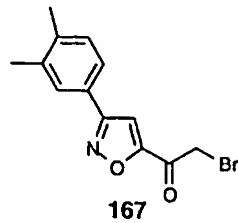
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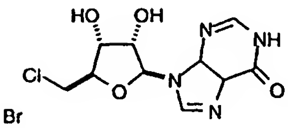
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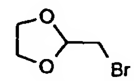
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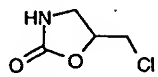
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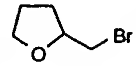
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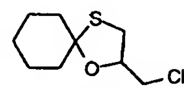
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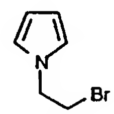
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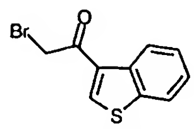
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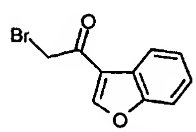
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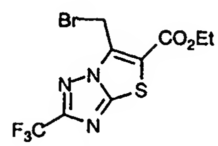
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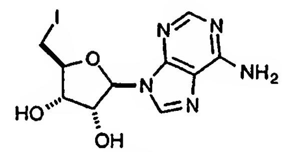
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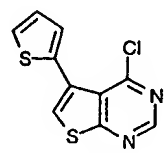
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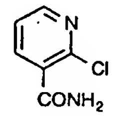
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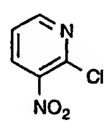
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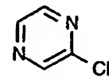
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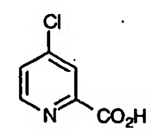
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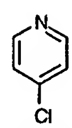
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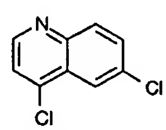
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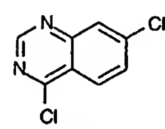
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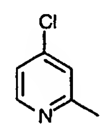
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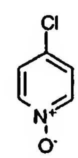
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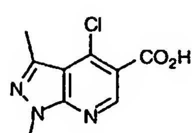
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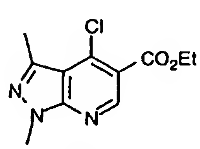
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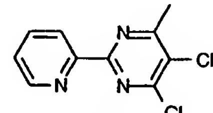
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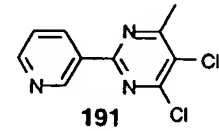
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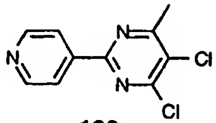
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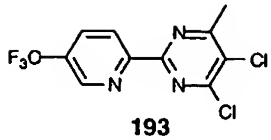
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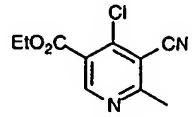
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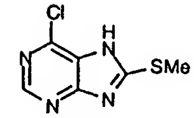
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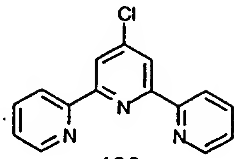
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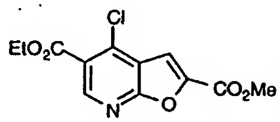
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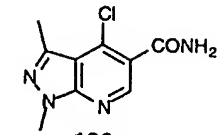
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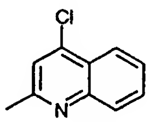
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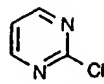
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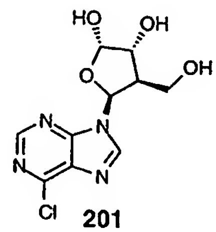
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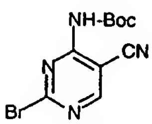
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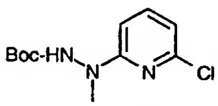
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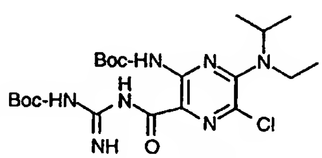
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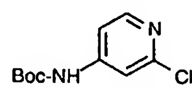
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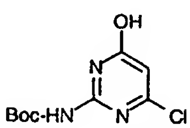
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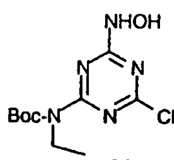
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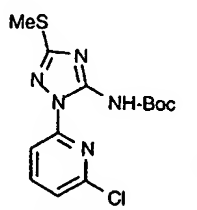
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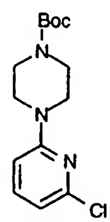
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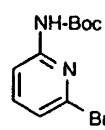
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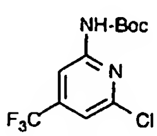
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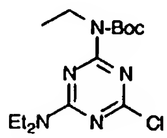
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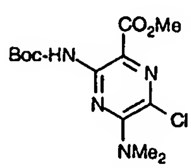
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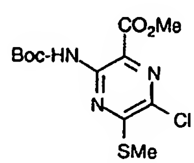
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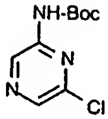
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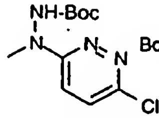
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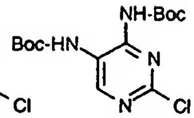
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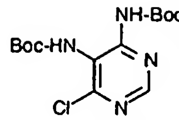
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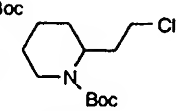
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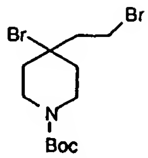
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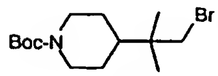
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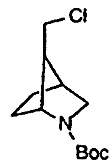
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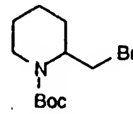
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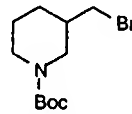
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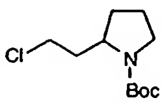
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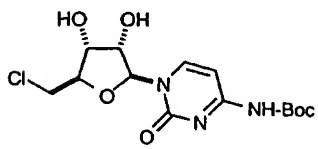
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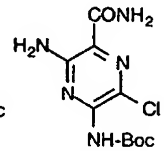
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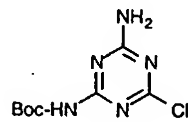
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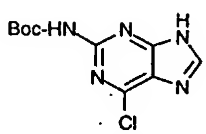
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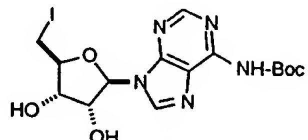
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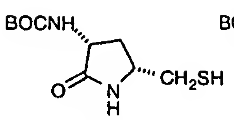
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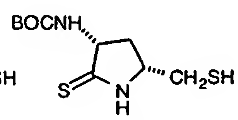
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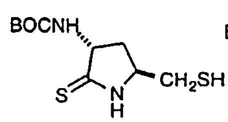
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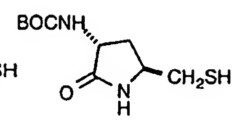
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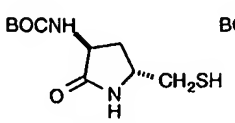
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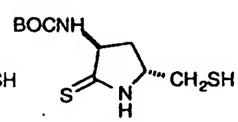
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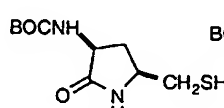
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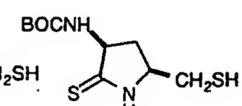
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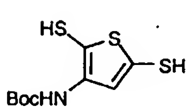
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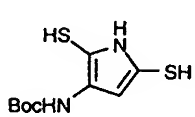
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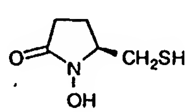
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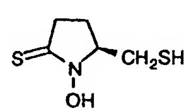
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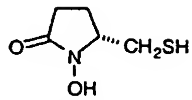

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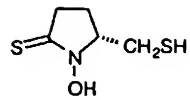

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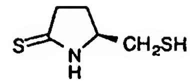

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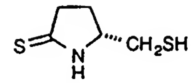

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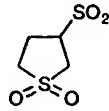
Table 18. Sulfonyl chlorides of the type A-SO_2Cl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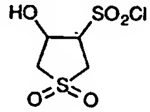
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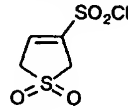
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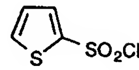
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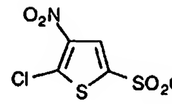
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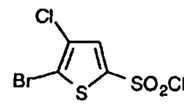
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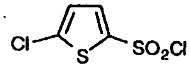
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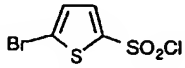
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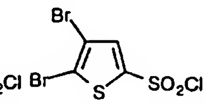
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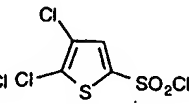
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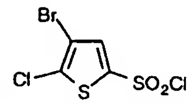
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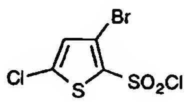
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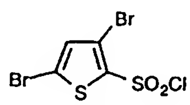
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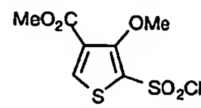
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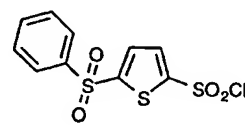
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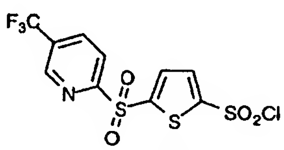
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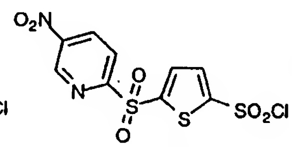
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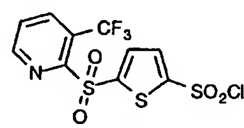
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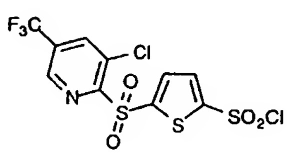
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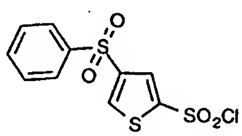
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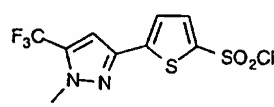
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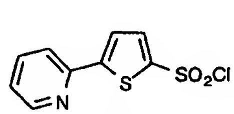
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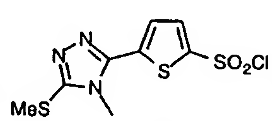
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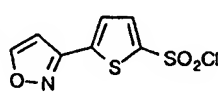
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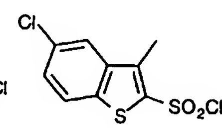
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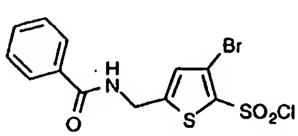
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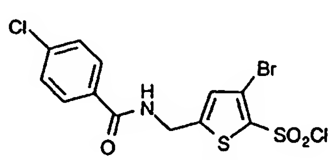
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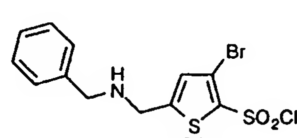
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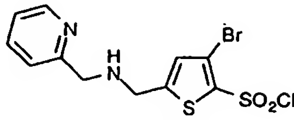
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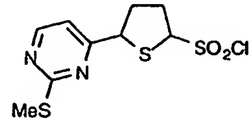
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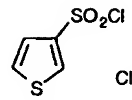
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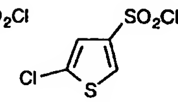
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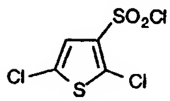
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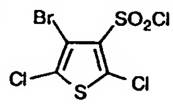
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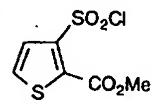
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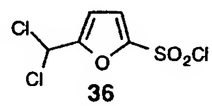
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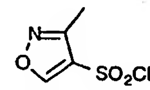
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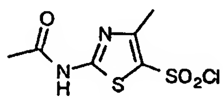
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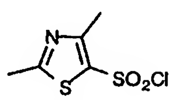
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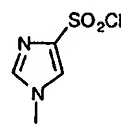
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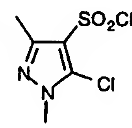
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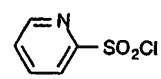
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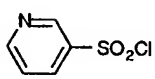
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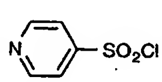
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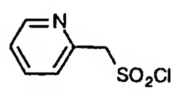
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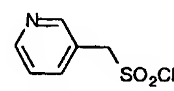
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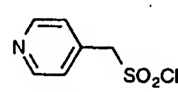
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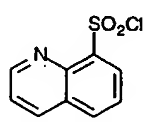
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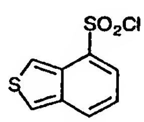
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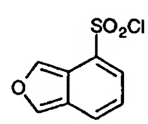
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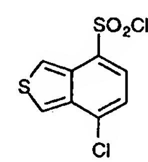
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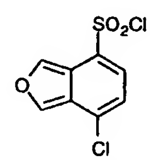
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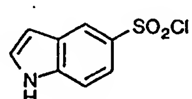
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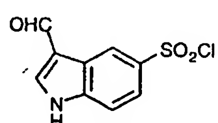
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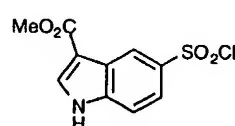
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The foregoing may be better understood by reference to the following examples which are provided for illustration and not intended to limit the scope of the inventive concept.

In Tables 2-10, the abbreviation bz=benzoyl, bn=benzyl, Ph=phenyl, BOC=t-butyloxycarbonyl and TS=p-toluenesulfonyl.

Compound 1

(3-(Aminomethyl)benzoyl)-Met-OCH_3

Step A

(3-(Chloromethyl)benzoyl)-Met-OCH_3

To a solution of methionine methyl ester hydrochloride (2.0 g, 10 mmol) and 3-(chloromethyl)benzoyl chloride (2.08 g, 11.0 mmol) in methylene chloride (50 mL) was slowly added triethylamine (3.07 mL, 22.0 mmol) at ice bath temperature for 2 hours. The mixture was washed with 0.5 N HCl (50 mL x 2), brine (50 mL x 2) and water (50 mL x 2) then dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to give the desired product (3.03 g) as a white solid: m.p. 82-83°C;
^{1}H NMR ($CDCl_3$) d 7.82 (1H, s), 7.74 (1H, d, J=7.7 Hz), 7.53 (1H, d, J=7.7 Hz), 7.42 (1H, t, J=7.7 Hz), 7.06 (1H, br d, J=7.6Hz), 4.92 (1H, ddd, J=7.6, 7.1, 5.1 Hz), 4.59 (2H, s), 3.78 (3H, s), 2.58 (2H, t, J=7.1Hz) 2.26 (1H, sm), 2.15 (1H, m), 2.10 (3H, s); ^{13}C NMR ($CDCl_3$) d 172.59, 166.54, 138.13, 134.25, 131.95, 129.12, 127.42, 126.97, 52.72, 52.14, 45.55, 31.47, 30.12, 15.55.

Step B

(3-(Azidomethyl)benzoyl)-Met-OCH_3

A suspension of (3-(chloromethyl)benzoyl)-Met-OCH_3 (1.58 g, 5.0 mmol) and sodium azide (1.3 g, 20.0 mmol) in DMSO (40 mL) was stirred at 80°C for 7 hours. The mixture was diluted with methylene chloride (100 mL), washed with brine (70 mL x 2) and water (70 mL x 2), and then dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give a yellow residue. Chromatography on silica gel (30% ethyl acetate in hexanes) to provide the desired product (1.45 g) as a colorless solid: m.p. 48-49°C; ^{1}H NMR ($CDCl_3$) d 7.78 (2H, m), 7.49 (2H, m), 6.99 (1H, br d, J=7.4 Hz), 4.49 (1H, ddd, J=7.4, 7.1, 5.2 Hz), 4.42 (2H, s), 3.80 (3H,s), 2.60 (2H, t, J=7.4 Hz), 2.29 (1H, m), 2.17 (1H, m), 2.12 (3H, s); ^{13}C NMR ($CDCl_3$) d 177.50. 166.54, 135.97, 134.06, 131.18, 128.89, 126.84, 126.71, 54.09, 52.47, 51.95, 31.38, 30.00,15.30.

Step C

(3-(Aminomethyl)benzoyl)-Met-OCH_3

A suspension of (3-(azidomethyl)benzoyl)-Met-OCH_3 (1.29 g, 4.0 mmol) and 5% palladium on carbon (0.2 g) in methanol (40 mL) was stirred under a hydrogen atmosphere (1 atm) for two days at room temperature. The catalyst was removed by filtration through celite (1.5 g) and the solvent was evaporated in vacuo. The residue was washed with water (5 mL x 2) and dried to give the desired product (1.12 g) as a colorless foam. ^{1}H NMR ($CDCl_3$) d 7.81 (1H, s), 7.68 (1H, d, J=7.4 Hz), 7.45 (1H, d, J=6.5 Hz), 7.36 (1H, t, J=7.4 Hz), 4.91 (1H, ddd, J=7.3, 7.1, 5.1 Hz), 3.90 (2H, s), 3.77 (3H, s), 3.21 (2H, br s), 2.59 (2H, t, J=7.4 Hz), 2.20 (1H, m), 2.12 (1H, m), 2.09 (3H, s).

Compound 2

(4-(Aminomethyl)benzoyl)-Met-OCH_3

The title compound is prepared according to the procedure used to prepare Compound 1 but replacing 3-(chloromethyl)benzoyl chloride with 4-(chloromethyl)benzoyl chloride.

Compound 3

(3-Aminobenzoyl)-Met-OCH_3

The title compound was prepared according to the procedure described in J. Biol. Chem. 269 12410-12413 (1994).

Compound 4

(4-Aminobenzoyl)-Met-OCH_3

Step A

N-BOC-4-Aminobenzoic acid

4-Aminobenzoic acid (10 g, 72.9 mmol) was placed into a mixture of dioxane (145.8 mL) and 0.5 M NaOH (145.8 mL). The solution was cooled to 0°C and di-t-butyl dicarbonate (23.87 g, 109.5 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The next day, the dioxane was removed, the residue was made acidic and extracted into ethyl acetate. The ethyl acetate fractions were combined and washed with 1N HCl to remove any unreacted starting material. The solution was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude material was recrystallized from ethyl acetate/hexanes to provide the desired product (12.2 g): m.p. 189-190°C; ^{1}H NMR (CD_3OD) d 1.52 (9H, s), 7.49 (2H, d, J=8.6 Hz), 7.91 (2H, d, J=8.6 Hz), 9.28 (1H, s); ^{13}C NMR (CD_3OD) d 28.59, 81.29, 118.54, 125.30, 131.81, 145.70, 155.00,

169.80; Anal. Calc. for $C_{12}H_{15}NO_4$, C: 60.76, H: 6.37, N: 5.90; Found, C: 60.52, H: 6.43, N: 5.83; HRMS Calc. for $C_{12}H_{15}NO_4$, 237.0961, Found, 237.1001.

<u>Step B</u>

<u>(N-BOC-4-Aminobenzoyl)-Met-OCH_3</u>

Into a dried, nitrogen filled flask was placed N-BOC-4-aminobenzoic acid (8.77 g, 36.97 mmol) in dry methylene chloride (148 mL) along with methionine methyl ester hydrochloride (8.12 g, 40.66 mmol). This solution was cooled in an ice bath and triethylamine (6.7 mL), EDCI (7.80 g, 40.66 mmol) and hydroxybenzotriazole (HOBT, 5.50 g, 40.66 mmol) were added. The mixture was stirred overnight, diluted with more methylene chloride and was extracted three times each with 1 M HCl, 1M $NaHCO_3$ and water. The methylene chloride was dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (9.72 g): m.p. 184-185°C; ^1H NMR ($CDCl_3$) d 1.53 (9H, s), 2.06-2.18 (4H, m), 2.23-2.33 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.80 (3H, s), 4.92 (1H, m), 7.45 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz); ^{13}C NMR ($CDCl_3$) d 15.59, 28.34, 30.15, 31.64, 52.10, 52.73, 81.20, 117.73, 127.8, 128.33, 141.88, 152.33, 166.50, 172.75; Anal. Calc. for $C_{18}H_{26}N_2O_5S$, C: 56.53, H: 6.85, N: 7.29; Found, C: 56.47, H: 6.86, N: 7.29; m/z (EI) 382 (M).

<u>Step C</u>

<u>(4-Aminobenzoyl)-Met-OCH_3 hydrochloride</u>

N-BOC-4-aminobenzoyl-Met-OCH_3 (3.53 g, 9.59 mmol) was placed into methylene chloride (30-35 mL) and to it was added 3M HCl/EtO_2 (38.4 mL). After standing, a white precipitate formed. After two hours the solution was decanted and the crystals were collected by centrifugation. The crystals were then washed several times with fresh ether and dried overnight on the vacuum pump. Meanwhile, the filtrate was left to stand overnight to allow additional product to precipitate. The second fraction was washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 2.87 g: m.p. 158-164°C; ^1H NMR ($CDCl_3$) d 2.10 (3H, s), 2.12-2.29 (1H, m), 2.52-2.71 (1H, m), 2.59 (2H, t, J=7.6 Hz), 3.75 (3H, s), 4.79 (1H, m), 7.02 (2H, d, J=8.6 Hz), 7.55 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) d 15.23, 31.43, 31.53, 52.91, 52.43, 124.35, 130.56, 135.31, 135.76, 168.95, 173.87; HRMS Calc. for $C_{13}H_{18}N_2O_3S$, 282.1038, Found 282.1009.

<u>Compound 5</u>

<u>(4-Amino-3-methylbenzoyl)-Met-OCH_3</u>

Step A

N-BOC-4-Amino-3-methylbenzoic acid

4-Amino-3-methylbenzoic acid (5 g, 33.1 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting orange-brown solid was recrystallized from ethyl acetate and hexanes to provide the desired product (4.99 g) as tan prismatic crystals: m.p. 180-182°C; 1H NMR (CD3OD) d 1.51 (9h, s), 2.27 (3H, s), 7.66 (1H, d, *J*=8.1 Hz), 7.79-7.82 (2H, m), 8.32 (1H, s); 13C NMR (CD3OD) d 17.98, 28.62, 81.47, 123.12, 127.05, 129.14, 130.65, 132.99, 142.45, 155.33, 168.70; Anal. Calc. for $C_{13}H_{17}NO_4$, C: 62.15, H: 6.82, N: 5.58; Found C: 62.07, H: 6.86, N: 5.46; m/z (EI) 251; HRMS Calc. for $C_{13}H_{17}NO_4$, 251.1158; Found, 251.1153.

Step B

(N-BOC-4-Amino-3-methylbenzoyl)-Met-OCH_3

N-BOC-4-amino-3-methylbenzoic acid (2.00 g, 7.96 mmol) was reacted with with methionine methyl ester hydrochloride (1.75 g, 8.76 mmol), triethylamine (1.4 mL), EDCI (1.68 g, 8.76 mmol) and hydroxybenzotriazole (HOBT, 1.18 g, 8.76 mmol) in dry methylene chloride (31.8 mL) according to the procedure described for the preparation of N-BOC-4-aminobenzoyl)-Met-OCH_3. The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (2.61 g): m.p. 163-165°C; ^{1}H NMR ($CDCl_3$) d 1.54 (9H, s), 2.06-2.18 (4H, m), 2.23-2.34 (4H, m), 2.59 (2H, t, *J*=6.8 Hz), 3.80 (3H, s), 4.92 (1H, m), 6.45 (1H, s), 6.88 (1H, d, *J*=7.5 Hz), 7.63 (1H, d, *J*=8.6 Hz), 7.66 (1H, s), 8.05 (1H, d, *J*=8.6 Hz); ^{13}C NMR ($CDCl_3$) d 15.47, 17.61, 28.22, 30.03, 31.55, 51.93, 52.57, 81.04, 118.73, 125.62, 127.66, 129.54, 139.89, 152.34, 166.58, 172.66.

Step C

(4-Amino-3-methylbenzoyl)-Met-OCH_3 hydrochloride

N-BOC-4-Amino-3-methylbenzoyl-Met-OCH_3 (0.99 g, 2.59 mmol) was dissolved in methylene chloride (15-20 mL) and precipitated with 3M HCl/Et_2O (20.7 mL). A pale orange precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.83 g: m.p. 157-159°C; ^{1}H NMR (CD_3OD) d 2.04 (3H, s), 2.11-2.25 (1H, m), 2.47 (3H, s), 2.52-2.68 (3H, m), 3.74 (3H, s), 4.75-4.80 (1H, m), 7.48 (1H, d, *J*=8.2 Hz), 7.81 (2H, d, *J*=8.2 Hz), 7.87 (1H, s); ^{13}C NMR (CD_3OD) d 15.23, 17.28, 31.43, 31.51, 52.91, 53.37, 124.41, 127.85,

131.99, 133.63, 134.14, 135.65, 169.05, 173.84; Anal. Calc. for $C_{14}H_{21}N_2O_3S$, C: 50.52, H: 6.36, N: 8.42; Found C: 50.71, H: 6.40, N: 8.34.

Compound 6
(4-Amino-3-methoxybenzoyl)-Met-OCH_3

Step A
N-BOC-4-Amino-3-methoxybenzoic acid

4-Amino-3-methoxybenzoic acid (1 g, 5.98 mmol) was reacted according to the same procedure as that used in the process for preparing N-BOC-4-aminobenzoic acid. The resulting solid was recrystallized from ethyl acetate and hexanes to provide the desired product (1.5 g) as tan crystals: m.p. 176-178°C; ^{1}H NMR (CD_3OD) d 1.52 (9H, s), 3.92 (3H, s), 7.56 (1H, s), 7.62 (1H, d, J=8.4Hz), 7.96 (1H, s), 8.03 (1H, d, J=8.4 Hz); ^{13}C NMR (CD_3OD) d 28.53, 56.35, 81.78, 112.01, 118.58, 124.20, 125.76, 133.84, 149.04, 154.20, 169.60; HRMS Calc. for $C_{13}H_{17}NO_5$, 267.1107; Found, 267.1103.

Step B
(N-BOC-4-Amino-3-methoxybenzoyl)-Met-OCH_3

N-BOC-4-amino-3-methoxybenzoic acid (0.35 g, 1.31 mmol) was reacted with with methionine methyl ester hydrochloride (0.9 g, 1.43 mmol) using EDCI according to the procedure described for the preparation of (N-BOC-4-aminobenzoyl)-Met-OCH_3.

The resulting solid was recrystallized from ethyl acetate/hexanes to yield the desired product (0.36 g): m.p. 163-165°C; ^{1}H NMR ($CDCl_3$) d 1.53 (9H, s), 2.09-2.18 (4H, m), 2.23-2.35 (1H, m), 2.60 (2H, t, J=6.9 Hz), 3.80 (3H, s), 3.93 (3H, s), 4.92 (1H, br s), 6.93 (1H, d, J=7.6 Hz), 7.25(1H, m), 7.31 (1H, d, J=10.2 Hz), 7.44 (1H, s), 8.15 (1H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) d 15.47, 28.23, 30.09, 31.48, 52.06, 52.54, 55.81, 80.82, 98.06, 109.38, 116.66, 119.31, 131.52, 147.23, 152.31, 166.57, 172.58; m/z (FAB) 413 (M + 1).

Step C
(4-Amino-3-methoxybenzoyl)-Met-OCH_3 hydrochloride

N-BOC-4-Amino-3-methoxybenzoyl-Met-OCH_3 (0.71 g, 1.79 mmol) was dissolved in methylene chloride (4 mL) and precipitated with 3M HCl/Et_2O (12 mL). A reddish precipitate was obtained, washed with ether and dried overnight on the vacuum pump. The total yield of the desired product was 0.55 g: m.p. 176-177°C; ^{1}H NMR (CD_3OD) d 2.08 (3H, s), 2.21 (2H, m), 2.61 (2H, m), 3.74 (3H, s), 4.02 (3H, s), 4.79 (1H, m), 7.50

(1H, d, J=8.2 Hz), 7.57 (1H, d, J=4.1 Hz), 7.67 (1H, s); ^{13}C NMR (CD_3OD) d 15.26, 31.34, 31.42, 52.95, 53.38, 57.12, 112.29, 121.43, 124.57, 124.77, 136.15, 153.67, 168.79, 173.81.

Compound 7
(4-Amino-1-naphthoyl)-Met-OCH_3

Step A
4-Amino-1-naphthoic acid

4-Amino-1-naphthalenecarbonitrile (1.5 g, 8.91 mmol) was suspended in a 50% KOH solution (18 mL). The heterogeneous solution was heated at reflux for 2-3 days. Once the solution became homogeneous and TLC showed no more starting material, the deep red solution was cooled and poured over 200 mL of water. The resulting solution was then filtered and the desired product was precipitated with concentrated HCl. The resulting red crystals were filtered and the filtrate was refiltered to give pink crystals. The first fraction of crystals was treated with activated carbon to remove some of the red color. A total of 1.51 g of the desired product was obtained: m.p. 169-171°C; ^{1}H NMR (CD_3OD) d 6.69 (1H, d, J=8.2 Hz), 7.38-7.43 (1H, m), 7.48-7.54 (1H, m), 8.03 (1H, d, J=8.5 Hz), 8.13 (1H, d, J=8.2 Hz), 9.09 (1H, d, J=8.5 Hz); ^{13}C NMR (CD_3OD) d 107.39, 114.61, 122.99, 123.92, 125.21, 127.40, 128.48, 135.04, 151.35, 171.44; HRMS Calc. for $C_{11}H_7NO_2$, 187.0633; Found, 187.0642.

Step B
N-BOC-4-Amino-1-naphthoic acid

4-Amino-1-naphthoic acid (0.86 g, 4.61 mmol) was dissolved in dioxane (9.2 mL). Di-t-butyl dicarbonate (1.11 g, 5.07 mmol) was added and the mixture was stirred overnight. The reaction mixture was worked up as described above for N-BOC-4-aminobenzoic acid to give 0.76 g of the desired product as a reddish pink solid: m.p. 194-195°C; ^{1}H NMR (CD_3OD) d 1.56 (9H, s), 7.53-7.62 (2H, m), 7.79 (1H, d, J=8.1 Hz), 8.12 (1H, d, J=8.0 Hz), 8.22 (1H, d, J=8.18 Hz), 9.02 (1H, d, J=8.9 Hz); ^{13}C NMR (CD_3OD) d 26.68, 81.62, 119.06, 123.40, 124.57, 127.03, 127.37, 128.49, 128.77, 131.89, 133.76, 139.86, 155.95, 170.73; Anal. Calc. for $C_{17}H_{17}NO_4$, C: 66.90, H: 5.96, N: 4.88; Found C: 66.49, H: 6.08, N: 4.79; m/z (EI), 289; HRMS Calc. for $C_{16}H_{17}NO_4$, 287.1158; Found, 287.1151.

Step C

(N-BOC-4-Amino-1-naphthoyl)-Met-OCH_3

N-BOC-4-Amino-naphthoic acid (0.46 g, 1.60 mmol), methionine methyl ester hydrochloride (0.35 g, 1.76 mmol), EDCI (0.43 g, 1.76 mmol), HOBT (0.24 g, 1.76 mmol) and triethylamine (0.27 mL) in methylene chloride (6.4 mL) were reacted as described above for N-BOC-4-aminobenzoyl-Met-OCH3. After workup and recrystallization from ethyl acetate hexanes, the desired product (0.44 g) was obtained as pale pink crystals: m.p. 131-132°C; ^{1}H NMR ($CDCl_3$) d 1.57 (9H, s), 2.11-2.21 (4H, m), 2.29-2.41 (1H, m), 2.65 (2H, t, J=7.1 Hz), 3.83 (3H, s), 4.99-5.06 (1H, m), 6.68 (1H, d, J=8.0 Hz), 7.02 (1H, s), 7.56-7.59 (2H, m) 7.69 (1H, d, J=7.9 Hz), 7.87-7.90 (1H, m), 8.02 (1H, d, J=7.9 Hz), 8.44-8.48 (1H, m); ^{13}C NMR ($CDCl_3$) d 15.56, 28.31, 30.19, 31.65, 52.06, 52.64, 81.17, 115.82, 120.18, 125.79, 126.37, 126.53, 127.18, 131.02, 135.65, 152.93, 169.04, 172.40; HRMS Calc. for $C_{22}H_{28}N_2O_5S$, 432.1719; Found, 432.1702; m/z (FAB) 433 (M+1).

Step D

(4-Amino-1-naphthoyl)-Met-OCH_3 hydrochloride

(N-BOC-4-Amino-1-naphtholyl)-Met-OCH_3 (0.57 g, 1.31 mmol) was deprotected with HCl/ether to yield the desired product (0.31 g) as a white solid: m.p. 178-181°C; ^{1}H NMR (CD_3OD) d 2.08-2.16 (4H, m), 2.20-2.30 (1H, m) 2.57-2.75 (2H, m) 3.82 (3H, s), 4.87-4.91 (1H, m), 7.59 (1H, d, J=7.5 Hz), 7.67 (1H, d, J=7.5 Hz) 7.71-7.80 (2H, m), 8.03 (1H, dd, J=7.1, 2.0 Hz), 8.35 (1H, dd, J=6.8, 1.8 Hz); ^{13}C NMR (CD_3OD) d 15.23, 31.40, 53.01, 53.33, 119.90, 122.20, 126.15, 127.41,127.77, 129.09, 129.31, 131.50, 132.33, 135.64, 171.77, 173.83; m/z (FAB), 369 (M+1).

Compound 8

(4-Amino-2-phenylbenzoyl)-Met-OCH_3

Step A

4-Nitro-2-phenyltoluene

2-Bromo-4-nitrotoluene (2.16 g, 10.00 mmol) and phenylboric acid (1.46 g, 12.00 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added $Pd(Ph_3P)_4$ (0.58 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O. The crude product was chromatographed on silica gel using hexanes as eluent. After recrystallization from ethanol, the desired product (1.23 g) was obtained as pale orange needles: m.p. 69-71°C; ^{1}H NMR ($CDCl_3$) d 2.36 (3H, s), 7.29-7.40 (2H, m), 7.41-7.49 (5H, m), 8.07-8.10 (2H, m); ^{13}C NMR ($CDCl_3$)

d 20.68, 121.96, 124.51, 127.78, 128.41, 128.83, 131.06, 139.06, 139.44, 142.97, 143.48, 146.05; Anal. Calc. for $C_{13}H_{11}NO_2$, C: 73.26, H: 5.20, N: 6.57; Found, C: 73.10, H: 5.12, N: 6.50; m/z (EI) 213; HRMS Calc. for $C_{13}H_{11}NO_2$, 213.0790; Found, 213.0793.

Step B
4-Nitro-2-phenylbenzoic acid

4-Nitro-2-phenyltoluene (0.5 g, 2.34 mmol) was dissolved in water (4.6 mL) and pyridine (2.3 mL). The mixture was heated to reflux and $KMnO_4$ (1.85 g, 11.7 mmol) was added. The reaction mixture was heated overnight and the solution was filtered and washed several times with boiling water. The aqueous solution was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solution was dried over Na_2SO_4 and the solvent removed in vacuo to provide the desired product (0.37 g): m.p. 174-176°C, ^1H NMR (CD_3OD) d 7.38-7.48 (5H, m), 7.96 (1H, d, J=8.5 Hz), 8.21 (1H, d, J=2.3 Hz), 8.28 (1H, dd, J=8.48, 2.37 Hz); ^{13}C NMR (CD_3OD) d 122.95, 126.09, 129.27, 129.42, 129.49, 131.56, 139.26, 140.42, 144.41, 150.17, 170.52; m/z (EI) 243 (M).

Step C
(4-Nitro-2-phenylbenzoyl)-Met-OCH_3

4-Nitro-2-phenylbenzoic acid (0.3 g, 1.23 mmol), methionine methyl ester hydrochloride salt (0.27 g, 1.35 mmol), EDCI (0.26 g, 1.35 mmol), HOBT (0.18 g, 1.35 mmol) and triethylamine (0.19 mL) in dry methylene chloride (4.9 mL) were reacted according the procedure described above for (N-BOC-4-aminobenzoyl)-Met-OCH_3. After recrystallization of the product from ethyl acetate hexanes, the desired product (0.41 g) was obtained: m.p. 98-101°C; ^1H NMR ($CDCl_3$) d 1.62-1.73 (1H, m), 1.79-1.88 (1H, m), 1.91 (3H, s), 1.99 (2H, t, J=7.2 Hz), 3.59 (3H, s), 4.53 (1H, m), 6.45 (1H, d, J=7.8 Hz), 7.33-7.40 (5H, m), 7.67 (1H, d, J=8.3 Hz), 8.07-8.12 (2H, m); ^{13}C NMR ($CDCl_3$) d 14.92, 29.11, 30.67, 51.51, 52.29, 121.86, 124.74, 128.27, 128.60, 128.69, 129.52, 137.50, 140.56, 141.02, 148.09, 167.23, 171.23; m/z (FAB), 389 (M+1).

Step D
(4-Amino-2-phenylbenzoyl)-Met-OCH_3

(4-Nitro-2-phenylbenzoyl)-Met-OCH_3 (0.35 g, 0.90 mmol) was dissolved in ethyl acetate (9.0 mL). To this mixture was added $SnCl_2 \cdot 2H_2O$ (1.02 g, 4.5 mmol) and the reaction mixture was heated under nitrogen at reflux for one hour. The mixture was poured onto ice, the solution was made basic using $NaHCO_3$ and the product was extracted into ethyl acetate several times (7-8). The ethyl acetate solutions were combined, washed with brine and

dried over Na_2SO_4. The solvent was removed in vacuo to the desired product (0.24 g) as a yellow solid: ^1H NMR ($CDCl_3$) d 1.58-1.70 (1H, m), 1.80-1.92 (1H, m), 1.98 (3H, s), 2.06 (2H, t, J=7.7 Hz), 3.62 (3H, s), 4.00 (2H, br s), 4.56-4.63 (1H, m), 5.84 (1H, d, J=7.7 Hz), 6.50 (1H, s), 6.61 (1H, d, J=8.4 Hz) 7.29-7.42 (5H, m), 7.58 (1H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) d 15.02, 29.25, 31.25, 51.57, 52.15, 113.27, 115.88, 123.52, 127.56, 128.37, 128.44, 130.92, 140.66, 141.44, 148.53, 168.58, 171.91.

Compound 9

(4-Amino-2-(2-thienyl)benzoyl)-Met-OCH_3

The title compound can be prepared according to the method used to prepare Compound 8, only substituting thiophene-2-boronic acid for phenyl boronic acid.

Compound 10

(4-Amino-2-(1-naphthyl)benzoyl)-Met-OCH_3

The title compound can be prepared according to the method used to prepare Compound 8, only substituting 1-naphthylboronic acid for phenylboronic acid.

Compound 11

4-Amino-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Compound 12

4-Amino-4'-biphenyl carboxylic acid

Step A

4-Nitro-4'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-4-methylbenzene.

Step B

4-Nitro-4'-biphenyl carboxylic acid

The title compound was prepared by $KMnO_4$ oxidation of 4-nitro-4'-methylbiphenyl.

Step C

4-Amino-4'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-4'-biphenyl carboxylic acid.

Compound 13

4-Amino-3'-biphenyl carboxylic acid

Step A

4-Nitro-3'-methylbiphenyl

The title compound was prepared by Suzuki coupling of 1-bromo-4-nitrobenzene and 1-bromo-3-methylbenzene.

Step B

4-Nitro-3'-biphenyl carboxylic acid

The title compound was prepared by $KMnO_4$ oxidation of 4-nitro-3'-methylbiphenyl.

Step C

4-Amino-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 4-nitro-3'-biphenyl carboxylic acid.

Compound 14

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

Step A

2-Methoxy-4-nitro-3'-methylbiphenyl

The title compound was prepared by reaction of 1-bromo-2-methoxy-4-nitrobenzene with 3-methylphenylboronic acid in the presence of palladium acetate.

Step B

2-Methoxy-4-nitro-3'-biphenylcarboxylic acid

The title compound was prepared by $KMnO_4$ oxidation of 2-methoxy-4-nitro-3'-methylbiphenyl.

Step C

4-Amino-2-methoxy-3'-biphenyl carboxylic acid

The title compound can be prepared by palladium catalyzed hydrogenation of 2-methoxy-4-nitro-3'-biphenyl carboxylic acid.

Compound 15

4-Amino-2-isopropyloxy-3'-biphenyl carboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

Compound 16

4-Amino-2-phenyl-3'-biphenylcarboxylic acid

The title compound can be prepared by methods analogous to those used to prepare Compound 14.

Compound 17

(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH_3

Step A

2-Bromo-4-nitrobenzoic acid

2-Bromo-4-nitrotoluene (5.0 g, 23.14 mmol) was dissolved in pyridine (23 mL) and water (46 mL). The heterogeneous mixture was heated to 60°C and $KMnO_4$ (18.29 g, 115.7 mmol) was added carefully. The mixture was then heated under reflux overnight. The reaction mixture was filtered and washed with boiling water. The solution was then made acidic and extracted into ethyl acetate, dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product was dissolved in aqueous NaOH and washed with hexanes. The aqueous phase was made acidic and the product was extracted into ethyl acetate. The ethyl acetate solutions were combined and dried over Na_2SO_4 and the solvent was removed in vacuo to provide the desired product (3.72 g): m.p. 158-160°C; ^{1}H NMR (CD_3OD) d 7.81 (1H, d, J=8.5 Hz), 8.08 (1H, d, J=8.5 Hz), 8.30 (1H, s); ^{13}C NMR (CD_3OD) d 121.96, 122.75, 129.36, 132.24, 139.52, 149.54, 167.75; Anal. Calc. for $C_7H_4BrNO_4$ •0.1 ethyl acetate, C: 34.88, H: 1.90, N: 5.50; Found, C: 34.68, H: 1.86, N: 5.82.

Step B

3,5-Dimethylphenylboronic acid

Magnesium turnings (1.44 g, 59.43 mmol) were coverd with dry THF (18.8 mL) in a dried, nitrogen filled flask fitted with an addition funnel and reflux condenser. To this was added 5-bromo-m-xylene (10 g, 54.03 mmol) in THF (15 mL) after initiation of the Grignard reaction. The addition was carried out over several minutes and the reacton mixture was heated at reflux for 1-2 hours until most of the magnesium had reacted. The reaction mixture was then cooled and transferred to an addition funnel fitted to an nitrogen

filled flask containing triisopropyl borate (24.9 mL) at -70°C. The dropwise addition was carried out over several minutes and the mixture warmed to room temperature and stirred overnight. The grey solution was poured onto 2 M HCl and immediately turned yellow. The solution was extracted with Et_2O and the Et_2O fractions were combined, dried over $MgSO_4$ and the solvent was removed in vacuo to provide the desired product (2.41 g): m.p.249-251°C; ^{1}H NMR ($CDCl_3$) d 2.44 (6H, s), 7.23 (1H, s), 7.84 (2H, s); ^{13}C NMR (CD_3OD) d 21.36, 133.28, 134.39, 137.48.

Step C

4-Nitro-2-(3,5-dimethylphenyl)benzoic acid

2-Bromo-4-nitrobenzoic acid (0.43 g, 2.03 mmol) and 3,5-dimethylphenyl boronic acid (0.334 g, 2.23 mmol) were dissolved in anhydrous DMF (25 mL) under nitrogen. To this mixture was added Cs_2CO_3 (1.66 g, 5.08 mmol) followed by $Pd(Ph_3P)_4$ (0.12 g, 5%). The mixture was heated at 100°C overnight. The solution was poured onto 1N HCl and extracted with Et_2O. It was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was chromatographed on silica gel using a 9:1 mixture of hexanes and ethyl acetate to provide the desired product (0.34 g): ^{1}H NMR ($CDCl_3$) d 2.36 (6H, s), 6.99 (2H, s), 7.07 (1H, s), 8.03 (1H, d, J=9.0 Hz), 8.23-8.25 (2H, m); ^{13}C NMR ($CDCl_3$) d 21.28, 121.68, 123.68, 125.74, 126.07, 130.22, 131.19, 131.31, 135.04, 138.21, 144.74, 170.75.

Step D

(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH_3

4-Nitro-2-(3,5-dimethylphenyl)benzoic acid (0.15 g, 0.55 mmol), methionine methyl ester hydrochloride (0.11 g, 0.55 mmol), EDCI (0.11 g, 0.55 mmol), HOBT (0.07 g, 0.55 mmol) and triethylamine (0.08 mL) in dry methylene chloride (2.2 mL) were reacted and worked up according to the procedure for (N-BOC-4-aminobenzoyl)- Met-OCH_3 as described above. After recrystallization from ethyl acetate and hexanes, the desired product was obtained (0.13 g): m.p. 122-124°C; ^{1}H NMR ($CDCl_3$) d 1.2-1.84 (1H, m), 1.85-1.97 (1H, m), 2.01 (3H, s), 2.05 (3H, t, J=7.7Hz), 2.38 (6H, s), 3.70 (3H, s), 4.67-4.74 (1H, m), 6.03 (1H, d, J=7.9 Hz), 7.05 (2H, s), 7.09 (1H, s), 7.84-7.87 (1H, m), 7.84-7.87 (1H, m) 8.23-8.26 (2H, m); ^{13}C NMR ($CDCl_3$) d 15.20, 21.26, 29.22, 31.15, 51.79, 52.57, 122.07, 125.11, 126.27, 130.03, 130.53, 137.77, 138.82, 140.29, 141.56, 148.41, 167.14, 171.53.

Step E

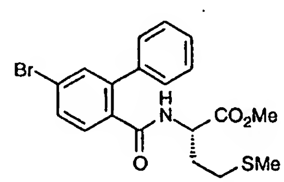
(4-Amino-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH_3

(4-Nitro-2-(3,5-dimethylphenyl)benzoyl)-Met-OCH_3 (0.11 g, 0.26 mmol) was dissolved in ethyl acetate (3.0 mL). To this mixture was added $SnCl_2 \cdot 2H_2O$ (0.3 g, 1.30 mmol) and the reacton was heated under nitrogen at reflux for 6 hours. The mixture was worked up as described above for (4-amino-2-phenylbenzoyl)-Met-OCH_3 to give the desired product (0.15 g): ^1H NMR ($CDCl_3$) d 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 1.99 (3H, s), 2.05 (2H, t, J=7.6 Hz), 2.33 (6H, s), 3.64 (3H, s), 3.93 (2H, br s), 4.61-4.64 (1H, m), 5.82 (1H, d, J=7.7 Hz), 6.49 (1H, d, J=2.3 Hz) 6.62 (1H, dd, J=8.4, 2.4 Hz), 6.98 (2H, s), 7.00 (1H, s), 7.65 (1H, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) d 15.08, 21.17, 29.28, 31.49, 51.70, 52.18, 113.30, 115.94, 123.55, 126.36, 129.32, 131.23, 138.15, 140.72, 141.92, 148.40, 168.45, 172.01.

Preparation 1

Anilines of the formula B-NH_2

The anilines from Table 1, entries 10-126 (B-NH_2) are prepared using the procedures for Compounds 1-18 with the exception that methionine methyl ester is replaced by methioninesulfone methyl ester, (S-Me)cysteine methyl ester, serine methyl ester, (O-Me)serine methyl ester, (O-Me)homoserine methyl ester, homoserine lactone, isoleucine methyl ester, leucine methyl ester, norleucine methyl ester, norvaline methyl ester, cyclohexylalanine methyl ester, phenylalanine methyl ester, or glutamic acid dimethyl ester.



Preparation 2

4-Bromo-2-phenylbenzoyl methionine methyl ester

Preparation 2A

4-Bromo-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous HBr is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 2B

4-Bromo-2-phenylbenzoic acid

To a solution of the resultant compound from Preparation 2A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Preparation 2C

4-Bromo-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Preparation 2B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Preparation 2D

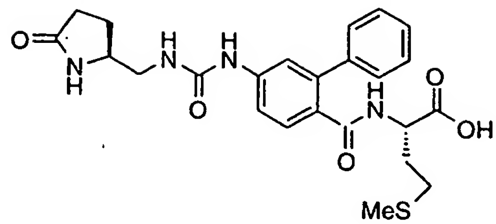
4-Bromo-2-phenylbenzoyl methionine methyl ester alternate procedure

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous HBr is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is treated with CuBr (1.1 equivalents) and heated. When judged complete by TLC analysis, the mixture is extracted into ethyl acetate which is dried and evaporated. The title arylbromide is purified by chromatography on silica gel.

Preparation 3

Arylbromides of the formula B-Br

The anilines from Table 1 ($B\text{-}NH_2$) are reacted according to the procedures of Preparation 2 to provide the arylbromides listed in Table 2.



Example 1

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

Example 1A

Methyl 4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoate

To a solution of methyl 4-amino-2-phenylbenzoate hydrochloride (1.0 equivalent) in toluene is added triphosgene (0.33 equivalent) and the mixture is heated at reflux until judged complete by TLC analysis. The intermediate is reacted without further purification with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (2.0 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1B

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoic acid

To a solution of the resultant compound from Example 1A (1.0 equivalent) in a 3:1 mixture of tetrahydrofuran (THF) and water is added an excess (1.5 equivalents) of LiOH. When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.

Example 1C

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 1B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 1D

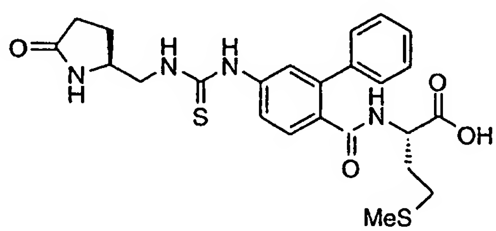
4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and triethylamine (2.0 equivalents). The intermediate is reacted without further purification with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 1E

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

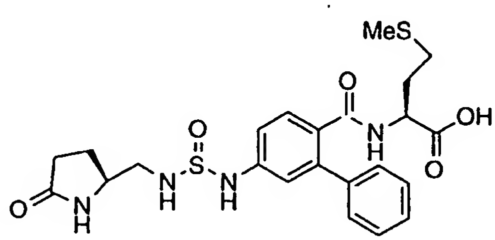
To a solution of the resultant compound from Example 1C in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 2

4-((*S*)-2-Pyrrolidone-5-aminomethylthiocarbonyl)amino-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 1 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 3

4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

Example 3A

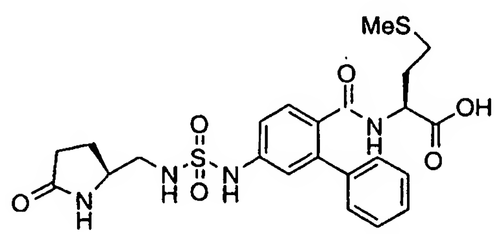
4-((S)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added thionyl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 3B

4-((*S*)-2-Pyrrolidone-5-aminomethylsulfinyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 3A in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 4

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine

Example 4A

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in methylene chloride is added sulfuryl chloride (1.0 equivalent) and triethylamine (2.0 equivalents). After the amine has fully reacted, (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is added. When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4B

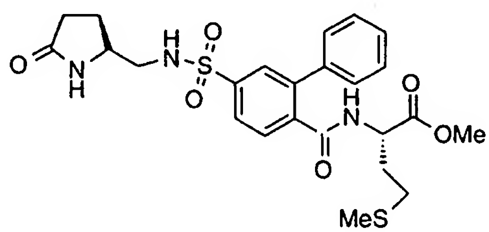
4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate procedure

A solution of 1 equivalent of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and sulfuryl chloride (1.0 equivalent) in acetonitrile with a catalytic amount of antimony(V) chloride is heated to reflux until judged complete by TLC analysis. The solution is then cooled, filtered, and all volatiles are removed under reduced pressure. The residue is taken up in dichloromethane and treated with triethylamine (1 equivalent and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent). When the reaction is judged complete by TLC analysis, the product is isolated as described in Example 1A and purified by chromatography on silica gel.

Example 4C

4-((S)-2-Pyrrolidone-5-aminomethylsulfonyl)amino-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 4A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 5

4-((*S*)-2-Pyrrolidone-5-methylaminosulfonyl)-2-phenylbenzoyl methionine

Example 5A

4-Chlorosulfonyl-2-phenylbenzoic acid methyl ester

To a solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists. The chlorodiazonium salt is poured into a solution of sulfur dioxide (10 equivalents), copper (II) chloride (0.5 equivalent) and KCl (1.1 equivalents) in dioxane. When TLC analysis indicated that the reaction is complete, the mixture is diluted with water and extracted into benzene which is dried and evaporated to give the title sulfonyl chloride

Example 5B

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 5A (1.0 equivalent) in methylene chloride is added (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 5C

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 5B is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 5D

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonyl)-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 5C (1.0 equivalent) in (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 5E

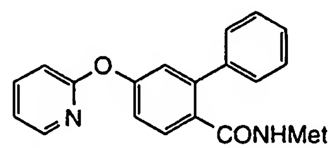
4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine methyl ester, alternate preparation

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in concentrated HCl is added a solution of sodium nitrite (1.1 equivalents) until an excess of nitrous acid persists at which time the chlorodiazonium salt will be treated with gaseous sulfur dioxide and copper (II) chloride to give the sulfonyl chloride (0.1 equivalent). This intermediate is reacted with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) according to the procedure of Example 5B to give the title compound.

Example 5F

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)amino-2-phenylbenzoyl methionine

To a solution of the resultant compound from Example 5D (1.0 equivalent) in a 3:1 mixture of THF and water is added an excess of LiOH (1.5 equivalents). When hydrolysis is judged complete by TLC analysis, the solvent is evaporated and the remaining aqueous layer is acidified to pH = 3 and extracted into ethyl acetate which is dried and evaporated prior to purification by chromatography on silica gel.



Example 6

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

Example 6A

4-Hydroxy-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 6B

4-(2-Pyridyloxy)-2-phenylbenzoic acid methyl ester

A solution of the resultant phenol from Example 6A (1.0 equivalent) is treated with 2-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K_2CO_3 (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6C

4-(2-Pyridyloxy)-2-phenylbenzoic acid

A solution of the resultant ester from Example 6B (1.0 equivalent) in aqueous methanol is treated with NaOH (2.0 equivalents) and stirred until the reaction is deemed complete by TLC analysis. The mixture is acidified, diluted with water, and extracted into ethyl acetate which is dried and evaporated. Chromatography on silica gel provides the title product.

Example 6D

4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 6C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 6E

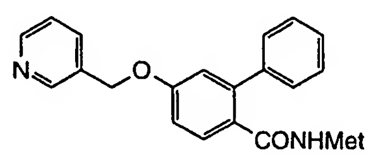
4-(2-Pyridyloxy)-2-phenylbenzoylmethionine methyl ester, alternate procedure

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) until an excess of nitrous acid persists to form the diazonium salt. This salt is then diluted further with water and heated to form the phenol which is purified by chromatography on silica gel. A solution of this phenol (1.0 equivalent) is treated with 3-bromopyridine (1.0 equivalent) in the presence of a NaH (1.0 equivalent), or K_2CO_3 (2.0 equivalents) and copper (1.0 equivalent) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 6F

4-(2-pyridyloxy)-2-phenylbenzoylmethionine

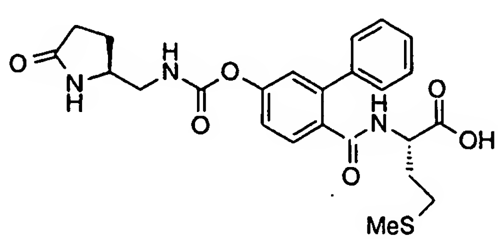
The resultant compound from Example 6E is hydrolyzed according to the procedure of Example 1B to give the title compound.



Example 7

4-(3-pyridylmethylenoxy)-2-phenylbenzoylmethionine

The title compound is prepared as described in Example 6 with the exception that 2-bromopyridine is replaced by 3-chloromethylpyridine hydrochloride.



Example 8

4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

Example 8A

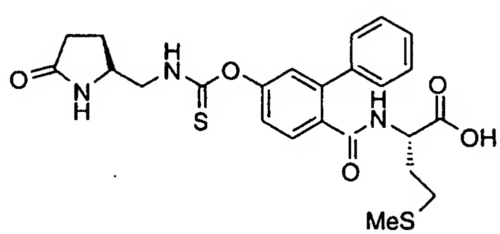
4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine methyl ester

To a solution of 4-hydroxy-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) from Example 6E in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The chloroformate is reacted without further purification with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 8B

4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonyloxy-2-phenylbenzoyl methionine

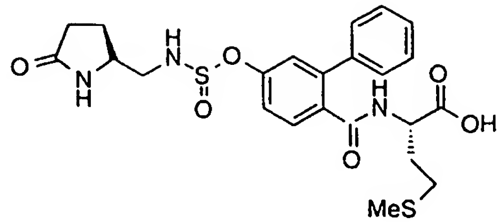
The resultant compound from Example 8A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 9

4-((*S*)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxy-2-phenylbenzoyl methionine methyl ester

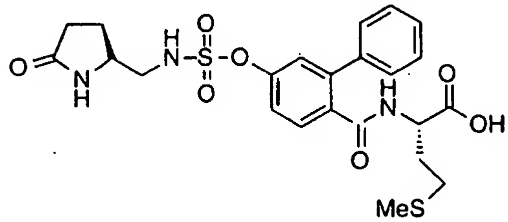
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thiophosgene.



Example 10

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfinyloxy)-2-phenylbenzoyl methionine

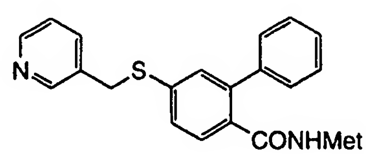
The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride.



Example 11

4-((S)-2-Pyrrolidone-5-aminomethyl)sulfonyloxy)-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride.



Example 12

4-(3-Pyridylmethylenthio)-2-phenylbenzoylmethionine

Example 12A

4-Mercapto-2-phenylbenzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoic acid (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is

treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel.

Example 12B

4-(2-Pyridylmethylenthio)-2-phenylbenzoic acid methyl ester

A solution of the resultant thiophenol (1.0 equivalent) from Example 12A is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12C

4-(2-Pyridylthiomethylen)-2-phenylbenzoic acid

The resultant compound from Example 12B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 12D

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 12C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 12E

4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The reaction is treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. The thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12F

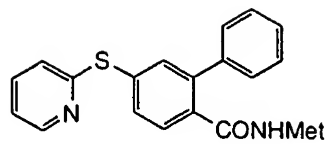
4-(2-Pyridylthiomethylen)-2-phenylbenzoylmethionine methyl ester, alternate procedure 2

Methyl 4-amino-2-phenylbenzoate (100 mmol) is mixed in 50% sulfuric acid, and is cooled by a ice-water bath. To the above mixture with good stirring is added slowly a cold solution of sodium nitrite (110 mmol) in water, the reaction temperature is kept under 10 °C. Powdered anhydrous sodium carbonate (100 mmol) is carefully added to the cold reaction mixture in small portions, until the reaction mixture reaches pH 7 to 8. Then, the reaction mixture is added in small portions to a solution of sodium p-methoxybenzylsulfide (prepared from reaction 110 mmol of p-methoxybenzylthiol with 55 mmol of 2.0 M NaOH aqueous solution). After completion of the addition, the reaction mixture is refluxed until judged complete by TLC analysis. The reaction mixture is then extracted with ether, and the organic extracts are washed sequentially with aqueous sodium carbonate solution, water and brine, dried with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The product thus obtained is dissolved in methanol and water , followed by addition of lithium hydroxide (200 mmol), and the mixture is refluxed until hydrolysis is judged complete by TLC analysis. The reaction mixture is then acidified with 6 N HCl, and extracted into ethyl acetate. The organic extracts are washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product obtained is redissolved in methylene chloride, followed by addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.1 equivalent) and 1-hydroxybenzotriazol (1.2 equivalent). The reaction is stirred until it is judged complete by TLC analysis, and then is diluted with ether. The mixture is washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. The resulting product is dissolved in trifluoroacetic acid and anisole (1.5 equivalent), and mercury diacetate (1.2 equivalent) is added. After TLC shows no starting material left, the reaction mixture is diluted with ether, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude material is purified by column chromatography to afford 2-phenyl-4-mercaptobenzoyl-methionine methyl ester. A solution of this thiophenol (1.0 equivalent) is treated with 2-chloromethylpyridine hydrochloride (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 12G

4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The resultant compound from Example 12D is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 13
4-(2-Pyridylthio)-2-phenylbenzoylmethionine

Example 13A
4-Fluoro-2-phenyl benzoic acid methyl ester

A solution of methyl 4-amino-2-phenylbenzoate (1.0 equivalent) in dilute aqueous HBF_4 is treated with $NaNO_2$ (1.1 equivalents) until an excess of nitrous acid persists. The mixture is extracted into ethyl acetate which is dried and evaporated. The title ester is purified by chromatography on silica gel.

Example 13B
4-Fluoro-2-phenyl benzoic acid

The resultant compound from Example 13A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 13C
4-Fluoro-2-phenyl benzoyl methionine methyl ester

The resultant product from Example 13B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13D
4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester

A mixture of the resultant fluorobenzoate from Example 13C (1.0 equivalent) and 2-mercaptopyridine (1.0 equivalent) is treated with K_2CO_3 (2.0 equivalents) or NaH (1.0 equivalent) in DMF or DMSO and is stirred until the reaction is judged complete by TLC analysis. The mixture is diluted with water and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 13E
4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 1

A solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dilute aqueous H_2SO_4 is treated with $NaNO_2$ (1.1 equivalents) to form the diazonium salt. The

reaction is treated with S_8 (10 equivalents) and heated. The mixture is extracted into ethyl acetate which is dried and evaporated. The title thiophenol is purified by chromatography on silica gel. A solution of this thiophenol (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalent), or K_2CO_3 (3.0 equivalent)s in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel.

Example 13F

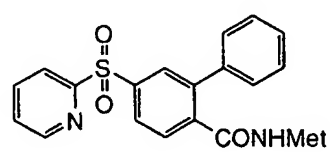
4-(2-Pyridylthio)-2-phenyl benzoyl methionine methyl ester, alternate procedure 2

A solution of the resultant thiophenol from Example 12A (1.0 equivalent) is treated with 2-bromopyridine hydrobromide (1.0 equivalent) in the presence of a NaH (2.0 equivalents), or K_2CO_3 (3.0 equivalents) in DMF or pyridine. The product is isolated by removal of the solvent and chromatography on silica gel. The resultant ester is hydrolyzed according to the procedure of Example 6C and then is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 13G

4-(2-Pyridylthio)-2-phenylbenzoylmethionine

The resultant compound from Example 13D is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 14

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

Example 14A

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid methyl ester

A solution of 4-(2-pyridylthio)-2-phenylbenzoic acid methyl ester (Example 13F) is carefully treated with two equivalents of *meta*-chloroperbenzoic acid in methylene chloride at low temperature and the reaction is then quenched with aqueous Na_2SO_3 when judged complete by TLC analysis. The layers are separated and the organic phase is extracted with

aqueous $NaHCO_3$ to remove the *m*-chlorobenzoic acid. The product is isolated by removal of the solvent and is purified by chromatography on silica gel.

Example 14B

4-(2-Pyridylsulfonyl)-2-phenylbenzoic acid

The resultant compound from Example 14A is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 14C

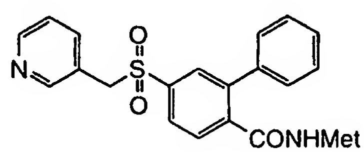
4-(2-pyridylsulfonyl)-2-phenylbenzoylmethionine methyl ester

The resultant product from Example 14B is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 14D

4-(2-Pyridylsulfonyl)-2-phenylbenzoylmethionine

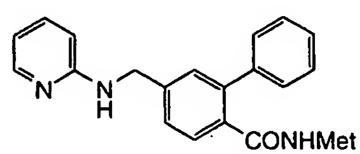
The resultant compound from Example 14C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 15

4-(3-Pyridylthiomethylen)-2-phenylbenzoylmethionine

The title compound is prepared from the resultant product of Example 12B using the procedures from Example 14.



Example 16

4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

Example 16A

2-Phenylterephthalic acid mono methyl ester

A solution of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), $Pd(OAc)_2$ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16B

4-(Hydroxymethyl)-2-phenylbenzoic acid methyl ester

The resultant acid from Example 16A (1.0 equivalent) is treated with a slight excess of N-methylmorpholine (1.1 equivalent) and isobutylchloroformate (1.0 equivalent) in THF at 0° C. The mixture is then treated with $NaBH_4$ (1.0 equivalent) and aqueous $NaHCO_3$ and stirred at 0° C until the reaction is judged complete by TLC analysis. The mixture is poured into dilute aqueous acid and extracted into ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 16C

4-(Hydroxymethyl)-2-phenylbenzoic acid

The resultant compound from Example 16B is hydrolyzed according to the procedure of Example 6C to give the title acid.

Example 16D

4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester

The resultant product from Example 16C is coupled to methionine methyl ester according to the procedure of Example 1C to give the title compound.

Example 16E

4-formyl-2-phenylbenzoyl methionine methyl ester

A mixture of the resultant alcohol from Example 16D (1.0 equivalent), N-methylmorpholine-N-oxide (1.5 equivalents), molecular sieves, and a catalytic amount of TPAP is stirred in a CH_2Cl_2/acetonitrile mixture until the reaction is judged complete by TLC analysis. The mixture is diluted with ethyl ether and filtered through SiO_2. The product is purified by chromatography on silica gel.

Example 16F

4-(formyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

A mixture of (2-phenyl-4-bromobenzoyl) methionine methyl ester (100 mmol), 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (100 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mmol) in toluene and 2 M sodium carbonate in water (100 mL) is heated at 80 °C until the starting methyl ester disappears. The resulting mixture is extracted with ether, and washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel. To a solution of the resulting vinyl compound in dioxane/water (4/1) is added osmium tetraoxide (0.03 equivalent), N-methylmorpholine N-oxide (3 equivalents), and the reaction is stirred at 25 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16G

4-(Hydroxymethyl)-2-phenylbenzoyl methionine methyl ester, alternate procedure

To a solution of the resultant compound from Example 16E in ethanol at 0 °C is added sodium borohydride (0.5 equivalent), and the reaction is stirred at 0 °C until TLC analysis shows the reaction to be complete. The reaction mixture is extracted with ether, which is washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to afford the title product.

Example 16H

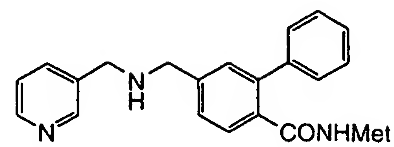
4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant aldehyde from Example 16E (1.0 equivalent), 2-aminopyridine (1.0 equivalent) and $NaCNBH_3$ (1.5 equivalents) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous $NaHCO_3$ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 16I

4-[(2-Aminopyridyl)methylene]-2-phenylbenzoylmethionine

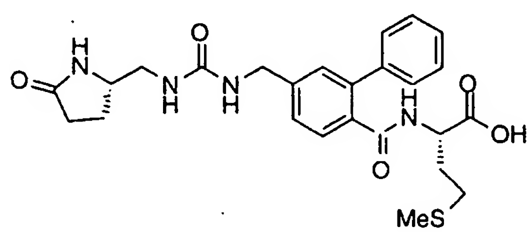
The resultant compound from Example 16H is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 17

4-[(3-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 16F-G and replacing 2-aminopyridine with 3-aminomethylpyridine affords the title product.



Example 18

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

Example 18A

4-(Azidomethyl)-2-phenylbenzoyl methionine methyl ester

To triphenylphosphine (1.0 equivalent) in tetrahydrofuran (THF) at -78° C is added diethyl azodicarboxylate (1.0 equivalent) in THF. To this mixture is added a solution of hydrazoic acid in benzene (2.0 equivalents) and then the resultant compound from Example 16D (1.0 equivalent). After one hour the mixture was warmed to room temperature, stirred until the reaction is judged complete by TLC analysis, evaporated and chromatographed on silica gel to afford the title product.

Example 18B

4-(Aminomethyl)-2-phenylbenzoyl methionine methyl ester

To the resultant compound from Example 18A in methanol is added triethylamine (3.0 equivalent) and propane 1,3-dithiol (3.0 equivalents). After the reaction is judged complete

by TLC analysis, the mixture is filtered and evaporated. Chromatography of the residue on silica gel provides the title product.

Example 18C

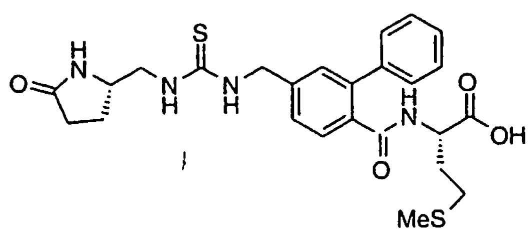
4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 18B (1.0 equivalent) in methylene chloride is added triphosgene (0.33 equivalent) and triethyl amine (2.0 equivalents). This intermediate is reacted without further purification with (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 18D

4-((*S*)-2-Pyrrolidone-5-aminomethylcarbonyl)aminomethyl-2-phenylbenzoyl methionine

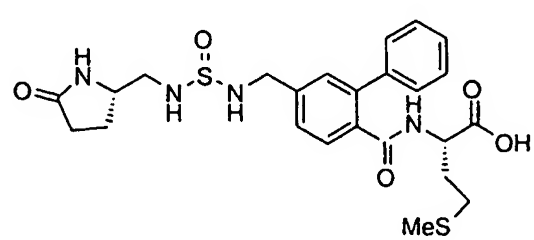
The resultant compound from Example 18C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 19

4-((*S*)-2-Pyrrolidone-5-aminomethylthiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

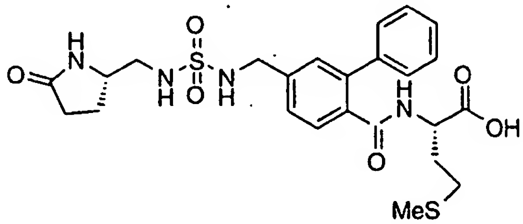
The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 20

4-((*S*)-2-Pyrrolidone-5-aminomethylsulfinyl)aminomethyl-2-phenylbenzoyl methionine

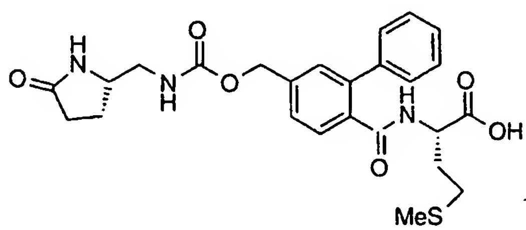
The title compound is prepared as described in Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent).



Example 21

4-((*S*)-2-Pyrrolidone-5-aminomethylsulfonyl)aminomethyl-2-phenylbenzoyl methionine

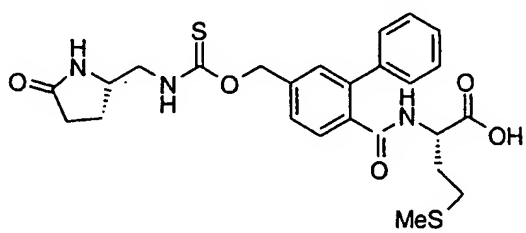
Using the Procedure of Example 4 with the resultant compound from Example 18B affords the title product.



Example 22

4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonyloxymethylene)-2-phenylbenzoyl methionine

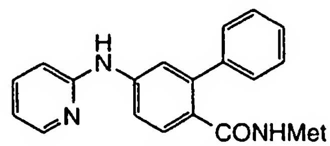
Using the procedure of Example 8 with the resultant compound from Example 16D provides the title product.



Example 23

4-((S)-2-Pyrrolidone-5-aminomethyl)thiocarbonyloxymethylene)-2-phenylbenzoyl methionine

Using the procedure of Example 8 with the resultant compound from Example 16D and replacing triphosgene (0.33 equivalent) with thiophosgene (1.0 equivalent) provides the title product.



Example 24

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

Example 24A

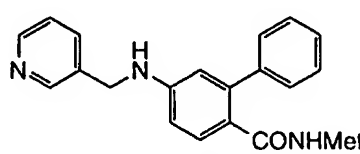
4-(2-Aminopyridyl)-2-phenylbenzoylmethionine methyl ester

4-Amino-2-phenylbenzoyl methionine (1.0 equivalent) methyl ester and 2-bromopyridine hydrobromide (1.0 equivalent) in pyridine are heated until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 24B

4-(2-Aminopyridyl)-2-phenylbenzoylmethionine

The resultant compound from Example 24A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 25

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

Example 25A

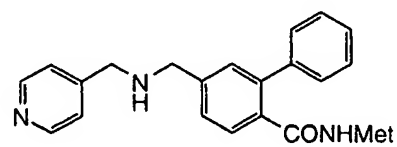
4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine methyl ester

A mixture of 3-pyridinecarboxaldehyde (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) and $NaCNBH_3$ (1.0 equivalent) in methanol/acetic acid is stirred until the reaction is judged complete by TLC analysis. The mixture is poured into aqueous $NaHCO_3$ and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title compound.

Example 25B

4-(3-Aminomethylpyridyl)-2-phenylbenzoylmethionine

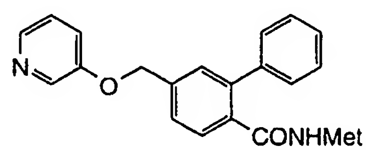
The resultant compound from Example 25A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 26

4-[(4-aminomethylpyridyl)methylene]-2-phenylbenzoylmethionine

Using the procedures of Examples 25 with the resultant amine from Example 18B and 3-pyridinecarboxaldehyde affords the title product.



Example 27

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

Example 27A

4-(*p*-Toluenesulfonyloxy)-2-phenylbenzoylmethionine methyl ester

The resultant compound from Example 16D (1.0 equivalent) and *p*-toluenesulfonyl chloride (1.0 equivalent) in pyridine are stirred until the reaction is judged complete by TLC analysis. The solvent is evaporated and the residue is taken up in ethyl acetate which is washed with water and brine, dried, and evaporated. Chromatography on silica gel affords the title product.

Example 27B

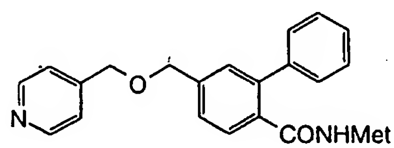
4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine methyl ester

3-Hydroxypyridine (1.0 equivalent) is treated with sodium hydride (1.0 equivalent) in DMSO, then the resultant compound from Example 27A (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 27C

4-(3-Pyridyloxymethylene)-2-phenylbenzoylmethionine

The resultant compound from Example 27B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 28

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine

Example 28A

4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester

Using the procedure of Example 27B but replacing 3-hydroxypyridine with 3-hydroxymethylpyridine affords the title compound.

Example 28B

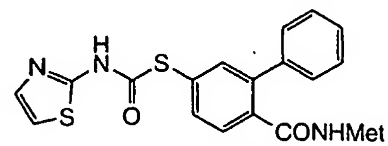
4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester, alternate procedure

The resultant compound from Example 16D (1.0 equivalent) is treated with sodium hydride (2.0 equivalents) in DMSO, then 3-chloromethylpyridine hydrochloride (1.0 equivalent) is added. When judged complete by TLC analysis, the reaction is diluted with water and ethyl acetate, the organic layer is dried and concentrated, and the crude title compound is purified by chromatography on silica gel.

Example 28C

<u>4-(3-Pyridylmethoxymethylene)-2-phenylbenzoylmethionine methyl ester</u>

The resultant compound from Example 28A is hydrolyzed according to the procedure of Example 1B to give the title product.



<u>Example 29</u>

<u>{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine</u>

<u>Example 29A</u>

<u>Thiazol-2-ylisocyanate</u>

A solution of 2-aminothiazol (1.0 mmol), triphosgene (0.34 mmol) and triethylamine (1.0 mmol) in toluene (10 mL) is refluxed until TLC shows no starting amine left. The solvent is then removed in vacuo, and the resulting material is used without further purification.

<u>Example 29B</u>

<u>{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester</u>

A solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1.0 mmol) and the isocyanate prepared in example 29A (1.0 mmol) in THF is refluxed until TLC shows no thiol left. The solvent is then evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

<u>Example 29C</u>

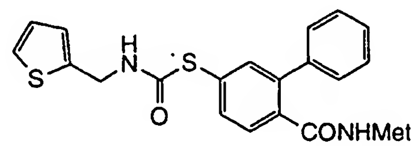
<u>{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine methyl ester, alternate procedure</u>

To a solution of 2-phenyl-4-mercaptobenzoyl-methionine methyl ester from example 12E or 12F (1 equivalent) in methylene chloride is added a solution of phosgene in toluene (1.0 equivalent) and *p*-dimethylaminopyridine (2.0 equivalents). When the reaction is judged complete by TLC analysis, the solvent is evaporated with toluene chasers. The thiochloroformate is reacted without further purification with 2-aminothiazol (1.0 equivalent) and triethylamine (1.0 equivalent) in dichloromethane. When judged complete by TLC analysis, the reaction is taken up in ethyl acetate and washed with 1N HCl and brine, evaporated, and purified by chromatography on silica gel.

Example 29D

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthio]benzoyl}-methionine

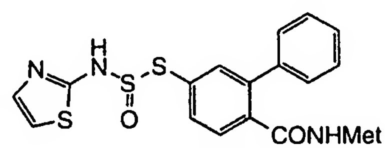
The resultant compound from Example 29B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 30

{2-Phenyl-4-[(thien-2-ylmethylamino)carbonylthio]benzoyl}-methionine

Using the procedure of Example 29 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 31

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

Example 31A

(N-Thionyl)thiazol-2-ylamine

A solution of 2-aminothiazol (1.0 mmol), in thionyl chloride is heated at reflux until the reaction is judged to be complete by TLC analysis. Then, the excess thionylchloride is distilled out in vacuo. The resulting material is used without further purification.

Example 31B

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester

Using the procedure of Example 29B but replacing the resultant product from Example 29A with the resultant product from Example 31A affords the title compound.

Example 31C

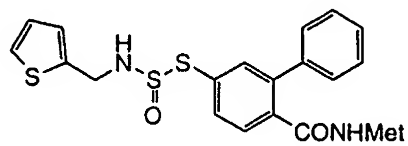
{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine methyl ester, alternate procedure

Using the procedure of Example 29C but replacing phosgene in toluene with thionyl chloride affords the title compound.

Example 31D

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthio]benzoyl}-methionine

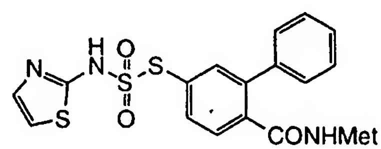
The resultant compound from Example 31B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 32

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthio]benzoyl}-methionine

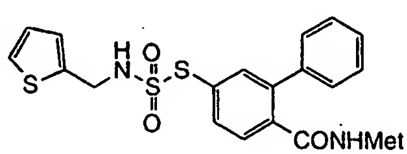
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 33

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthio]benzoyl}-methionine methyl ester

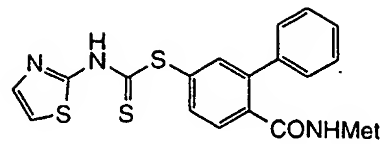
Using the procedure of Example 31 but replacing thionyl chloride with sulfuryl chloride affords the title product.



Example 34

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthio]benzoyl}-methionine

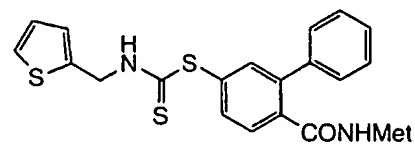
Using the procedure of Example 31 but replacing 2-aminothiazol with thien-2-ylmethylamine and replacing thionyl chloride with sulfuryl chloride affords the title product.



Example 35

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthio]benzoyl}-methionine

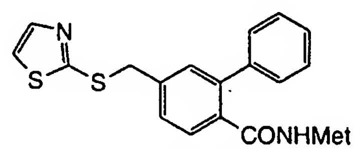
Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



Example 36

{2-Phenyl-4-[(thien-2-ylmethylamino)thiocarbonylthio]benzoyl}-methionine

Using the procedure of Example 29 and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 37

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

Example 37A

{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester

The resultant product from Example 27A is dissolved DMF/water (2/1), and sodium hydrosulfide (5 equivalent) is added to the reaction mixture. The reaction is stirred until TLC analysis shows that the reaction is complete. Then, the reaction mixture is acidified with 3 N HCl to about pH 4, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified with column chromatography on silica gel to give the title compound.

Example 37B

{2-Phenyl-4-[thiomethyl]benzoyl}-methionine methyl ester, alternate procedure

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16D (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K_2CO_3 (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

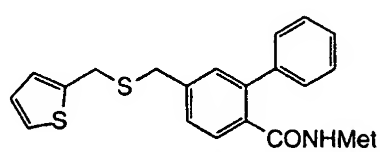
Example 37C

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine methyl ester

A mixture of the resultant thiol from Example 37A (1 mmol), 2-bromothiazole (1.5 mmol), and anhydrous potassium carbonate (5 mmol) in DMF is stirred at 100 °C until TLC analysis shows that the starting thiol disappeared. Then, the reaction mixture is diluted with water, extracted with ether, and washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by column chromatography on silica gel to give the title compound.

{2-Phenyl-4-[(thiazol-2-yl)thiomethyl]benzoyl}-methionine

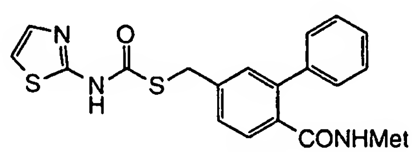
The resultant compound from Example 37C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 38

{2-Phenyl-4-[(thien-2-ylmethyl)thiomethyl]benzoyl}-methionine

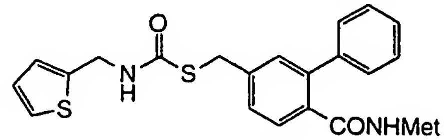
Using the procedure of Example 37 and replacing 2-bromothiazole with 2-bromomethylthiophene affords the title product.



Example 39

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

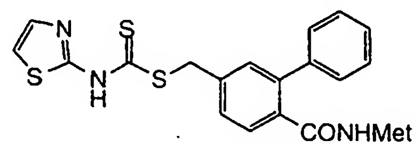
Using the procedure of Example 29 with the resultant product from Example 37A affords the title product.



Example 40

{2-Phenyl-4-[(thiazol-2-ylamino)carbonylthiomethyl]benzoyl}-methionine

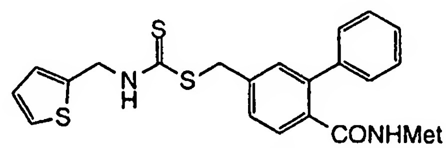
Using the procedure of Example 29 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 41

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

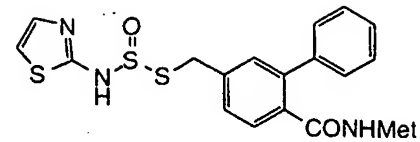
Using the procedure of Example 29 with the resultant product from Example 37A and replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol) affords the title product.



Example 42

{2-Phenyl-4-[(thiazol-2-ylamino)thiocarbonylthiomethyl]benzoyl}-methionine

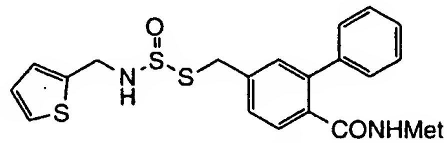
Using the procedure of Example 29 with the resultant product from Example 37A, replacing triphosgene (0.34 mmol) or a solution of phosgene in toluene (1.0 equivalent) with thiophosgene (1.0 mmol), and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 43

{2-Phenyl-4-[(thiazol-2-ylamino)thionylthiomethyl]benzoyl}-methionine

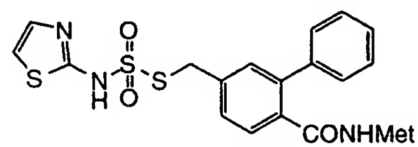
Using the procedure of Example 31 with the resultant product from Example 37A affords the title product.



Example 44

{2-Phenyl-4-[(thien-2-ylmethylamino)thionylthiomethyl]benzoyl}methionine

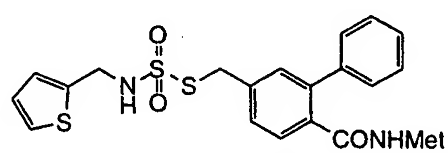
Using the procedure of Example 31 with the resultant product from Example 37A and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 45

{2-Phenyl-4-[(thiazol-2-ylamino)sulfonylthiomethyl]benzoyl}-methionine

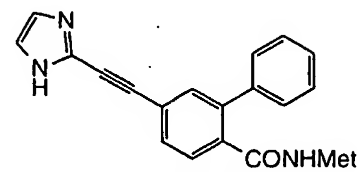
Using the procedure of Example 31 with the resultant product from Example 37A and replacing thionyl chloride with sulfuryl chloride affords the title product. affords the title product.



Example 46

{2-Phenyl-4-[(thien-2-ylmethylamino)sulfonylthiomethyl]benzoyl}-methionine

Using the procedure of Example 31 with the resultant product from Example 37A, replacing thionyl chloride with sulfuryl chloride, and replacing 2-aminothiazol with thien-2-ylmethylamine affords the title product.



Example 47

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}methionine

Example 47A

(4-Ethynyl-2-phenylbenzoyl)methionine methyl ester

A mixture of (2-phenyl-4-bromobenzoyl)-methionine methyl ester (100 mmol), diethylamine (300 mmol), trimethylsilylacetylene (110 mmol), bis(triphenylphosphine) palladium diacetate (5 mmol) and copper(I) iodide (3 mmol) in toluene is heated at 60 °C until TLC analysis indicates the starting methyl ester has disappeared. The reaction mixture is concentrated in vacuo, redissolved in ether, filtered through silica gel, and concentrated. The residue is then dissolved in THF, and is treated with tetrabutylammonium fluoride (120 mmol). After TLC analysis indicates that no starting material is left, the reaction mixture is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified with column chromatography on silica gel to give the title product.

Example 47B

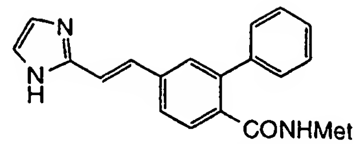
{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

The resultant product from Example 47A (5 mmol) is mixed with 4-bromoimidazole (5 mmol), diethylamine (1 mL), bis(triphenylphosphine) palladium diacetate (0.1 mmol) and copper(I) iodide (0.1 mmol) in toluene. The mixture is stirred at 25 °C until TLC analysis indicates the reaction is complete. The reaction mixture is concentrated in vacuo, and the residue is purified with column chromatography on silica gel to give the title product.

Example 47C

{4-[2-(Imidazol-2-yl)ethynyl]-2-phenylbenzoyl}-methionine

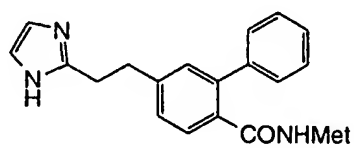
The resultant compound from Example 47B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 48

{4-[2-(Imidazol-4-yl)ethenyl]-2-phenylbenzoyl}-methionine

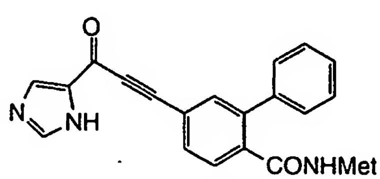
The resultant acetylene (3 mmol) from Example 47 is mixed with Lindlar catalyst (50 mg), 5 drops of quinoline in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 49

{4-[2-(Imidazol-4-yl)ethyl]-2-phenylbenzoyl}-methionine

The resultant olefin (1 mmol) from Example 48 is mixed with 5% palladium on carbon (100 mg) in ethyl acetate. The reaction mixture is attached to a hydrogenation apparatus, and then is detached from the apparatus after about 95% of the theoretical hydrogen has been absorbed. The reaction mixture is filtered and concentrated in vacuo. The crude product is purified with a column chromatography on silica gel to give the title compound.



Example 50

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

Example 50A

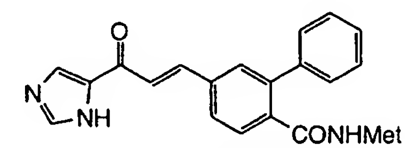
{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine methyl ester

A stainless autoclave containing the resultant product from Example 47A (5 mmol), 4-bromoimidazole (5 mmol), 1,1'-bis(diphenylphosphine)-ferrocenepalladium dichloride (0.1 mmol), and triethylamine (10 mL) is flushed with nitrogen, and pressurized to 20 atm with carbon monoxide. The reaction mixture is stirred at 120 °C until judged complete by TLC analysis. After cooling, the triethylamine is evaporated in vacuo, and the residue is purified by column chromatography on silica gel to give the title compound.

Example 50B

{4-[2-(Imidazol-4-ylcarbonyl)ethynyl]-2-phenylbenzoyl}-methionine

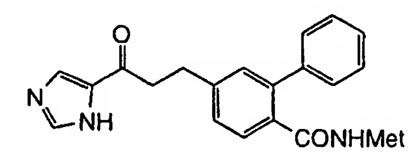
The resultant compound from Example 50A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 51

{4-[2-(Imidazol-4-ylcarbonyl)ethenyl]-2-phenylbenzoyl}-methionine

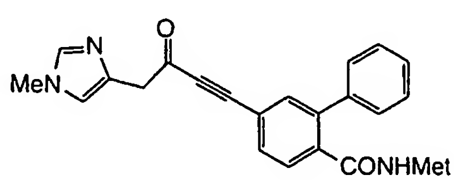
Using the procedure of Example 48 with the resultant compound from Example 50 affords the title product.



Example 52

{4-[2-(Imidazol-4-ylcarbonyl)ethyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 51 affords the title product.



Example 53

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}methionine

Example 53A

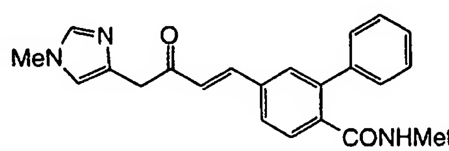
{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine methyl ester

To a solution of 1-methyl-4-imidazoleacetic acid (5 mmol) in methylene chloride at 0 °C is added oxalyl chloride (6 mmol) and DMF (0.05 mmol). After 30 minute, the solvent is evaporated in vacuo. The residue is redissolved in dichloromethane, followed by the addition of the resultant acetylene from Example 47A (5 mmol), triethylamine (10 mmol), and copper(I) iodide (1 mmol). The reaction is stirred at 25 °C until TLC analysis indicates no starting material is left in the reaction mixture. The reaction is diluted with ether, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue is then purified by column chromatography on silica gel to give the title compound.

Example 53B

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butynyl]-2-phenylbenzoyl}-methionine

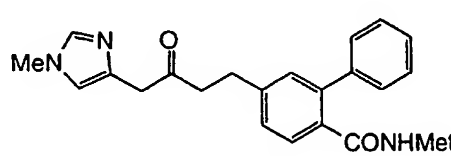
The resultant compound from Example 53A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 54

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butenyl]-2-phenylbenzoyl}-methionine

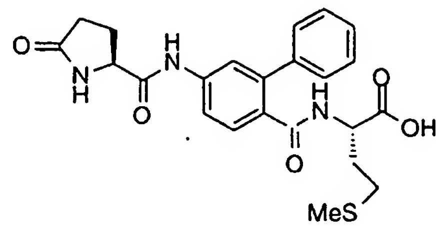
Using the procedure of Example 48 with the resultant compound from Example 53 affords the title product.



Example 55

{4-[4-(1-Methylimidazol-4-yl)-3-keto-1-butyl]-2-phenylbenzoyl}-methionine

Using the procedure of Example 49 with the resultant compound from Example 53 affords the title product.



Example 56

(*S*) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Example 56A

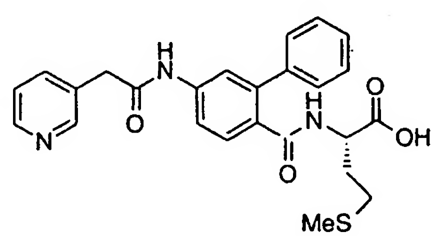
(*S*) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine methyl ester

To a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 56B

(*S*) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

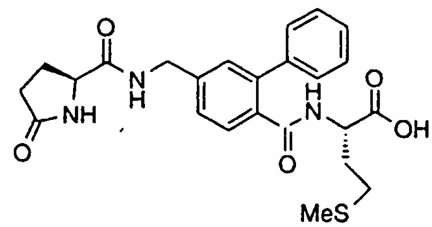
The resultant compound from Example 56A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 57

(*S*) Pyroglutamyl-(4-amino-2-phenyl)benzoyl methionine

Using the procedure of Example 56 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



Example 58

(*S*) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

Example 58A

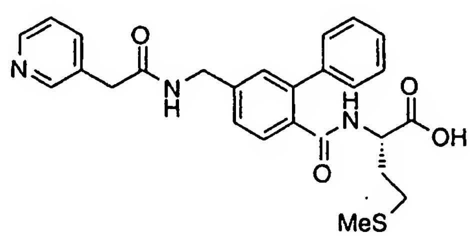
(*S*) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine methyl ester

To a solution of the resultant amine from Example 18B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by pyroglutamic acid (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 58B

(*S*) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

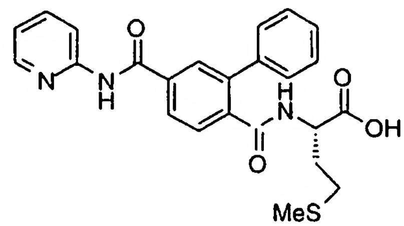
The resultant compound from Example 58A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 59

naming error(*S*) Pyroglutamyl-(4-aminomethyl-2-phenyl)benzoyl methionine

Using the procedure of Example 58 and replacing pyroglutamic acid with 3-pyridylacetic acid affords the title product.



Example 60

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

Example 60A

4-Carboxy-2-phenylbenzoyl methionine methyl ester

A solution of 4-bromo-2-phenylbenzoyl methionine methyl ester (1.0 equivalent), $Pd(OAc)_2$ (0.05 equivalent) and DPPE (1.0 equivalent) is heated in DMF to 65° C under 4 atm. of carbon monoxide until TLC analysis indicates that the reaction is complete. The reaction mixture is poured into water and extracted with ethyl acetate which is dried and evaporated. The product is purified by chromatography on silica gel.

Example 60B

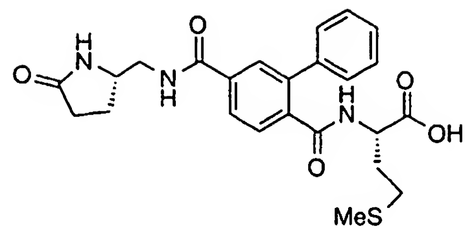
4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant acid from Example 60A (1.0 equivalent) in DMF is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed by 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 60C

4-[(Pyridin-2-ylamino)carbonyl]-2-phenylbenzoyl methionine

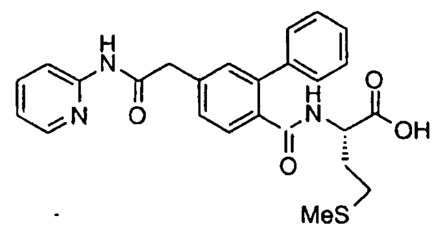
The resultant compound from Example 60B is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 61

4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonyl)-2-phenylbenzoyl methionine

Using the procedure of Example 60 and replacing 2-aminopyridine with (*S*)-5-aminomethyl-2-pyrrolidone affords the title product.



Example 62

4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

Example 62A

4-Diazocarbonyl-2-phenylbenzoyl methionine methyl ester

The resultant acid from Example 60A (1 equivalent) in dichloromethane is treated with oxalyl chloride (1 equivalent) and DMF (0.05 equivalent). When gas evolution has ceased, the acid chloride solution is added to an ether solution of diazomethane. The reaction is stirred until judged complete by TLC analysis, and then is concentrated to give the crude title compound which is purified by chromatography on silica gel.

Example 62B

4-carboxymethyl-2-phenylbenzoyl methionine methyl ester

The resultant compound from Example 62A (1 equivalent) in dioxane is added to a slurry of sodium thiosulfate (1.1 equivalents) and silver (I) oxide (0.5 equivalent) in water. The reaction is stirred until judged complete by TLC analysis, filtered, acidified, and extracted into ethyl acetate which is dried and evaporated. Chromatography of the residue on silica gel affords the title product.

Example 62C

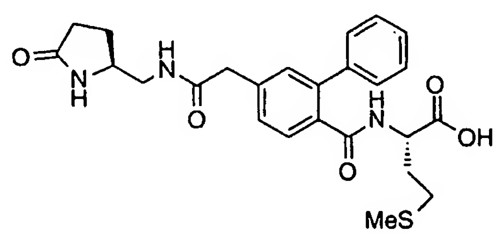
4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant acid from Example 62B (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by 2-aminopyridine (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 62D

4-[(Pyridin-2-ylamino)carbonylmethyl]-2-phenylbenzoyl methionine

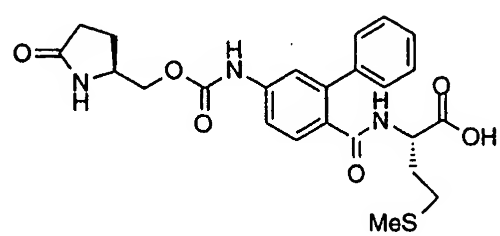
The resultant compound from Example 62C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 63

4-((*S*)-2-Pyrrolidone-5-aminomethyl)carbonylmethyl)-2-phenylbenzoyl methionine

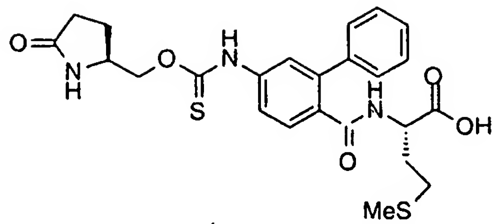
Using the procedure of Example 62 and replacing 2-aminopyridine with (*S*)-5-aminomethyl-2-pyrrolidone affords the title product.



Example 64

4-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)amino-2-phenylbenzoyl methionine

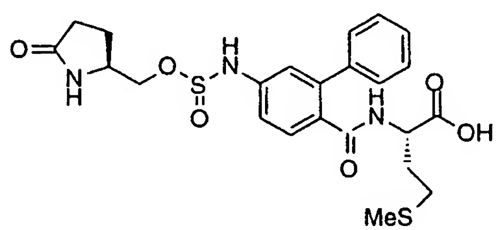
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 65

4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)amino-2-phenylbenzoyl methionine

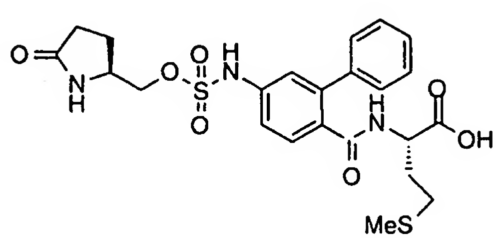
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 66

4-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)amino-2-phenylbenzoyl methionine

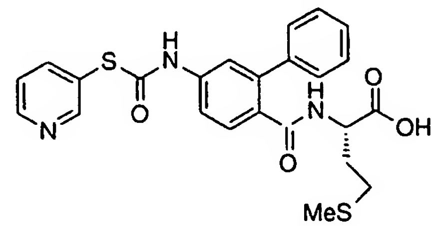
The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 67

4-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)amino-2-phenylbenzoyl methionine

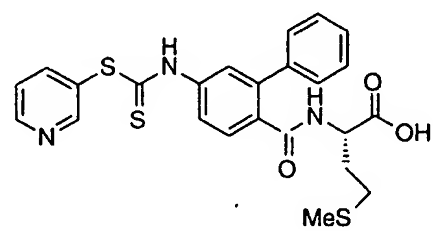
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 68

4-(Pyridin-3-ylmercaptocarbonyl)amino-2-phenylbenzoyl methionine

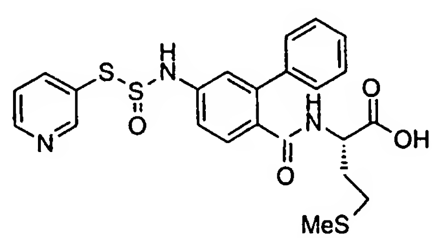
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 69

4-(Pyridin-3-ylmercaptothiocarbonyl)amino-2-phenylbenzoyl methionine

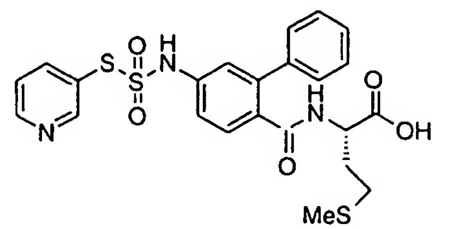
The title compound is prepared as described in Example 1 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 70

4-(Pyridin-3-ylmercaptosulfinyl)amino-2-phenylbenzoyl methionine

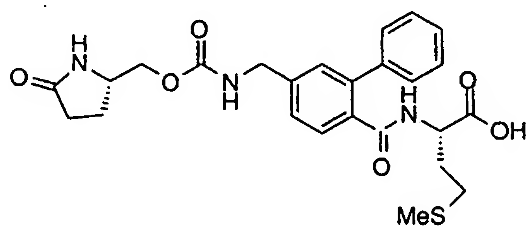
The title compound is prepared as described in Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 71

4-(Pyridin-3-ylmercaptosulfonyl)amino-2-phenylbenzoyl methionine

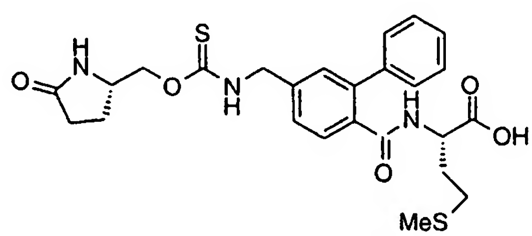
The title compound is prepared as described in Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 72

4-((*S*)-2-Pyrrolidone-5-methoxycarbonyl)aminomethyl-2-phenylbenzoyl methionine

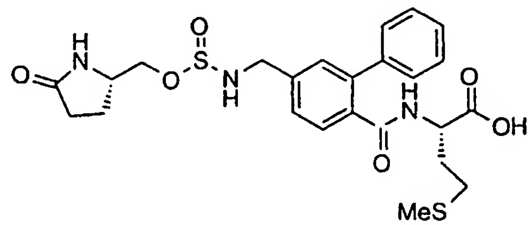
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 73

4-((*S*)-2-Pyrrolidone-5-methoxythiocarbonyl)aminomethyl-2-phenylbenzoyl methionine

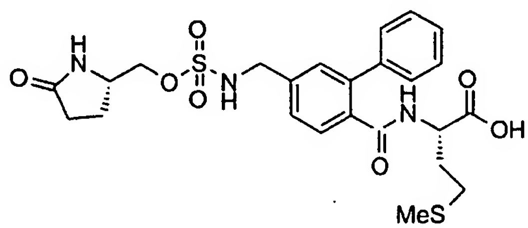
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 74

4-((*S*)-2-Pyrrolidone-5-methoxysulfinyl)aminomethyl-2-phenylbenzoyl methionine

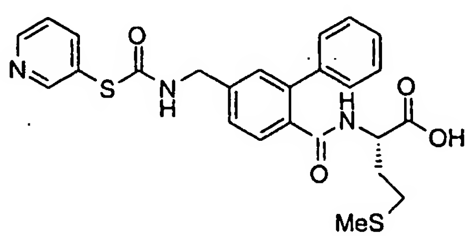
The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 75

4-((*S*)-2-Pyrrolidone-5-methoxysulfonyl)aminomethyl-2-phenylbenzoyl methionine

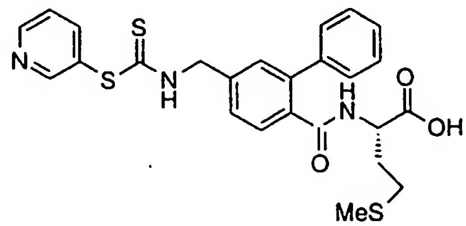
The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by (*S*)-5-hydroxymethyl-2-pyrrolidone (1.0 equivalent) and CuCl (0.1 equivalent).



Example 76

4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

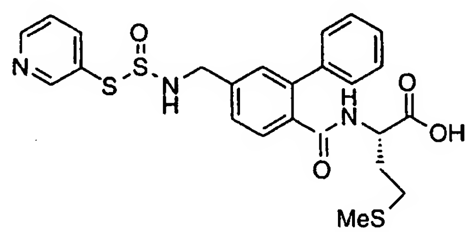
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 77

4-(Pyridin-3-ylmercaptocarbonyl)aminomethyl-2-phenylbenzoyl methionine

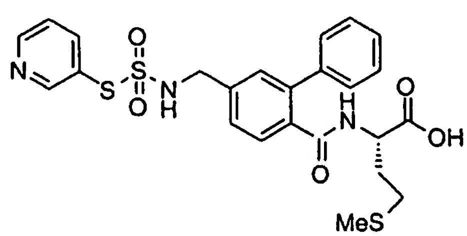
The title compound is prepared as described in Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent).



Example 78

4-(Pyridin-3-ylmercaptosulfinyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 3 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).



Example 79

4-(Pyridin-3-ylmercaptosulfonyl)aminomethyl-2-phenylbenzoyl methionine

The title compound is prepared as described in Example 4 using the resultant amine from Example 18B with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by 3-mercaptopyridine (1.0 equivalent).

Example 80
A-NH-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 ($A-NH_2$). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 81
A-NH-CS-NH-B

The procedure of Example 1 is used with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent), 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 ($A-NH_2$). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 82
A-NH-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and (*S*)-5-

aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 83

A-NH-SO_2-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 84

A-NH-SO_2-B

The procedure of Example 5 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 85

A-NH-CO-O-B

The anilines from Table 1 (B-NH_2) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 86

A-NH-CS-O-B

The anilines from Table 1 (B-NH_2) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 87

A-NH-SO-O-B

The anilines from Table 1 (B-NH_2) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thionyl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 88

A-NH-SO_2-O-B

The anilines from Table 1 (B-NH_2) are reacted according to the procedure of Example 6E. The resultant phenols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by sulfuryl chloride and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 89

A-NH-CH_2-B

The procedure of Example 16 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 90

A-NH-CO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 91

A-NH-CS-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 92

A-NH-SO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by thionyl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 93

A-NH-SO_2-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that triphosgene (0.33 equivalent) is replaced by sulfuryl chloride (1.0 equivalent) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 94

A-NH-CO-O-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 95

A-NH-CS-O-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 8 with the exception that phosgene in toluene is replaced by thiophosgene and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 96

A-NH-CO-S-B

The anilines Table 1 ($B-NH_2$) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 ($A-NH_2$). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 97

A-NH-CS-S-B

The anilines Table 1 ($B-NH_2$) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 ($A-NH_2$). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 98

A-NH-SO-S-B

The anilines Table 1 ($B-NH_2$) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 ($A-NH_2$). For products derived from

amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 99

A-NH-SO_2-S-B

The anilines Table 1 (B-NH_2) are converted into the corresponding mercaptans according to the procedure of Example 12E. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 100

A-NH-CO-S-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that 2-aminothiazol is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 101

A-NH-CS-S-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thiophosgene and 2-aminothiazol is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 102

A-NH-SO-S-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by thionyl chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 103

A-NH-SO_2-S-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding mercaptans according to the procedures of Examples 27A and 37A. These mercaptans are reacted according to the procedure of Example 29 with the exception that phosgene in toluene is replaced by sulfuryl

chloride and 2-aminothiazol is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 104

A-CO-NH-B

The procedure of Example 56 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and pyroglutamic acid is replaced by an acid from Table 4 (A-CO_2H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 105

A-CO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 58 with the exception that pyroglutamic acid is replaced by an acid from Table 4 (A-CO_2H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 106

A-CO-C≡C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 53 with the exception that 1-methyl-4-imidazoleacetic acid is replaced by an acid from Table 4 (A-CO_2H). For products derived from acids 164-238 and 262-269 from Table 4, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 107

A-CO-CH=CH-B

The products from Example 106 are reacted according to the procedure of Example 54. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 108

A-CO-CH_2-CH_2-B

The products from Example 107 are reacted according to the procedure of Example 55. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 109

A-NH-CO-B

The procedure of Example 60 is used with the exception that 4-bromo-2-phenylbenzoyl methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 2-aminopyridine is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 110

A-NH-CO-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 60A. The resultant carbocyclic acids are reacted according to the procedure of Example 62 with the exception that 2-aminopyridine is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 111

A-CH_2-NH-B

The procedure of Example 25 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an amine from Table 1 (B-NH_2) and 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is

followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

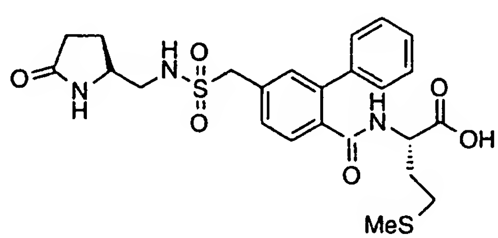
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 112

A-CH_2-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 25 with the exception that 3-pyridinecarboxaldehyde is replaced by an aldehyde from Table 5 (A-CHO). For products derived from aldehydes 360-432 and 433-440 from Table 5, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 113

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl methionine

Example 113A

4-Thioacetoxymethyl-2-phenylbenzoic acid methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 16B (1. equivalent) in THF. The reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K_2CO_3 (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 113B

4-Chlorosulfonylmethylene-2-phenylbenzoic acid methyl ester

The resultant compound from Example 113A in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 113C

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid methyl ester

To a solution of the resultant compound from Example 113B (1.0 equivalent) in methylene chloride is added (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 113D

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoic acid

The resultant compound from Example 113C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 113E

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine methyl ester

To a solution of the resultant compound from Example 113D (1.0 equivalent) in dimethylformamide (DMF) is added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (1.5 equivalents) followed by methionine methyl ester (1.0 equivalent) and 1-(3-dimehtylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 equivalents). When judged

complete by TLC analysis, the reaction is taken up in ethyl acetate which is washed with 1N HCl and saturated brine, and then is dried and evaporated. The crude reaction mixture is purified by column chromatography to afford the title product.

Example 113F

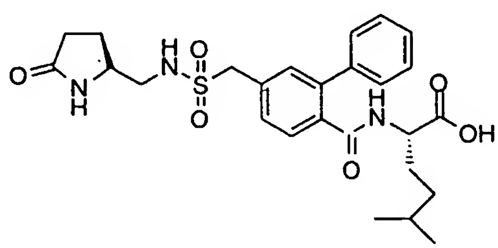
4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl methionine

The resultant compound from Example 113E is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 114

A-NH-SO_2-CH_2-B

The procedure of Example 113 is used with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.



Example 115

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethyl)-2-phenylbenzoyl leucine

Example 115A

4-(Hydroxymethyl)-2-phenylbenzoyl leucine methyl ester

(2-phenyl-4-bromobenzoyl)-leucine methyl ester is reacted according to the procedures of Example 16F-G.

Example 115B

4-Thioacetoxymethyl-2-phenylbenzoyl leucine methyl ester

To triphenylphosphine (1.2 equivalents) in THF at -78 °C is added diethylazodicarboxylate (1.2 equivalents) in THF. After 10 min thiolacetic acid (1.3 equivalents) in THF is added followed by the resultant compound from Example 115A (1. equivalent) in THF. The

reaction is stirred at -78 °C for 1 h and then at ambient temperature until it is judged to be complete by TLC analysis. The mixture is evaporated and the residue is taken up in methanol and is treated with K_2CO_3 (2 equivalents). When the reaction is judged to be complete by TLC analysis, the solvent is evaporated and the residue is chromatographed on silica gel to afford the title product.

Example 115C

4-Chlorosulfonylmethylene-2-phenylbenzoyl leucine methyl ester

The resultant compound from Example 115B in water is stirred vigorously while gaseous chlorine is bubbled through the mixture. When the reaction is judged to be done by TLC analysis, the reaction is extracted with dichloromethane which is dried and evaporated to afford the title product.

Example 115D

4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine methyl ester

To a solution of the resultant compound from Example 115C (1.0 equivalent) in methylene chloride is added (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) and triethylamine (1.0 equivalent). When the reaction is judged complete by TLC analysis, the solvent is evaporated and the residue is purified by chromatography on silica gel.

Example 115E

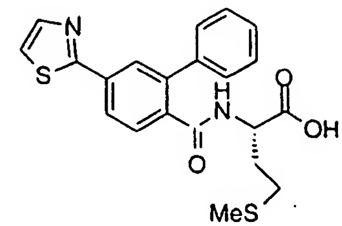
4-((*S*)-2-Pyrrolidone-5-aminomethyl)sulfonylmethylene-2-phenylbenzoyl leucine

The resultant compound from Example 115D is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 116

A-NH-SO_2-CH_2-B

The procedure of Example 115 is used with the exception that (2-phenyl-4-bromobenzoyl)-leucine methyl ester is replaced by a bromide from Table 2, entries 28-132 (B-Br) and (*S*)-5-aminomethyl-2-pyrrolidone is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.



Example 117

4-(2-Thiazolyl)-2-phenylbenzoyl methionine

Example 117A

2-Thiazole boronic acid

A solution of thiazole (1.0 equivalent) is lithiated with a slight excess of n-butyl lithium in THF (1.05 equivalents) and then treated with trimethyl borate (1.05 equivalents). The reaction mixture is quenched by the addition of aqueous HCl and the resulting boronate ester is cleaved by the addition of excess aqueous NaOH. After acidification and extraction into ethyl acetate the crude boronic acid is used without further purification.

Example 117B

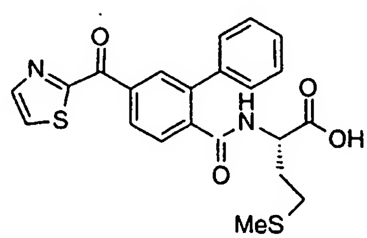
4-(2-Thiazolyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid (1.0 equivalent) and catalytic $Pd(PPh_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3. After cooling, the resulting biaryl compound is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 117C

4-(2-Thiazolyl)-2-phenylbenzoyl methionine

The resultant compound from Example 117C is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 118

4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

Example 118A

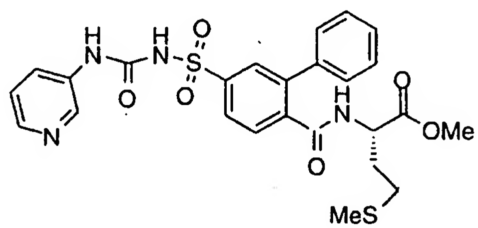
4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine methyl ester

A mixture of 4-bromo-2-phenylbenzoic acid methyl ester (1.0 equivalent), 2-thiazole boronic acid from Example 117A (1.0 equivalent) and catalytic $Pd(PPh_3)_4$ is heated in a two phase system of toluene and aqueous Na_2CO_3 previously purged with a large excess of carbon monoxide. The resulting diaryl ketone is isolated by evaporation of the organic phase and is purified by chromatography on silica gel.

Example 118B

4-(2-Thiazolylcarbonyl)-2-phenylbenzoyl methionine

The resultant compound from Example 118A is hydrolyzed according to the procedure of Example 1B to give the title product.



Example 119

4-[(3-Aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

Example 119A

4-Aminosulfonyl-2-phenylbenzoylmethionine methyl ester

To a solution of 4-chlorosulfonyl-2-phenylbenzoyl methionine methyl ester from Example 5E in dichloromethane is added aqueous ammonia and the mixture is stirred until the reaction is judged complete by TLC analysis. The organic phase is separated, dried and evaporated and the product is purified by chromatography on silica gel.

Example 119B

4-Isocyanatosulfonyl-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant sulfonamide from Example 119A in chlorobenzene is treated with with oxalyl chloride according to the procedure of Franz et al. (*J. Org. Chem*, 1964, 29, 2592) to give the title compound.

Example 119C

4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine methyl ester

A mixture of the resultant isocyanate from Example 119B (1 equivalent) in dichloromethane is treated with 3-aminopyridine (1 equivalent) and stirred until the reaction is judged complete by tlc analysis. The solvent is evaporated and the product is purified by chromatography on silica gel.

Example 119D

4-[(A-aminopyridyl)carbonylaminosulfonyl]-2-phenylbenzoylmethionine

The resultant compound from Example 119C is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 120

A-NH-CO-NH-SO_2-B

The anilines from Table 1 (B-NH_2) are reacted according to the procedures of Example 5E to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 121

A-NH-CO-NH-SO_2-CH_2-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 115A-C to afford the corresponding sulfonyl chlorides. These are reacted according to the procedure of Example 119 with the exception that 3-aminopyridine is replaced by an amine from Table 3 (A-NH_2). For products derived from amines 146-206 from Table 3, the final LiOH hydrolysis step also hydrolyzes the ester on the fragment of the final compound that is derived from amines 146-206.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 122

A-O-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 27 with the exception that 3-hydroxypyridine is replaced by an alcohol from Table 6 (A-OH). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 123

A-O-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 124

A-O-CS-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2), (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 125

A-O-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 126

A-O-SO_2-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH,

1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 127

A-O-CO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 128

A-O-CS-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by

removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 129

A-O-SO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 130

A-O-SO_2-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by an alcohol from Table 6 (A-OH, 1.0 equivalent) and CuCl (0.1 equivalent). For products derived from alcohols 280-359 and 408-431 from Table 6, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane

and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 131

A-S-B

The anilines from Table 1 ($B-NH_2$) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 132

A-S-CO-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the

anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 133

A-S-CS-NH-B

The procedure of Example 1 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2), (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH), and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 134

A-S-SO-NH-B

The procedure of Example 3 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 135

A-S-SO_2-NH-B

The procedure of Example 4 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and (*S*)-5-aminomethyl-2-pyrrolidone (1.0 equivalent) is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 136

A-S-CO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 137

A-S-CS-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 18 with the

exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH) and triphosgene (0.33 equivalent) is replaced by thiophosgene (1.0 equivalent). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 138

A-S-SO-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 3 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 139

A-S-SO_2-NH-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G and 18A-B. The resultant amines are reacted according to the procedure of Example 4 with the exception that (*S*)-5-aminomethyl-2-pyrrolidone is replaced by a mercaptan from Table 7 (A-SH). For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 140

A-O-B

The procedure of Example 6 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and 3-bromopyridine is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 141

A-S-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B-NH_2$) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 142

A-NH-B

The procedure of Example 24 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 (B-NH_2) and 2-bromopyridine hydrobromide is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 143

A-O-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 28 with the exception that 3-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 144

A-S-CH_2-B

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl; sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 145

A-C≡C-B

The procedure of Example 47 is used with the exception that (2-phenyl-4-bromobenzoyl)-methionine methyl ester is replaced by a bromide from Table 2 (B-Br) and 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 146

A-CH=CH-B

The products from Example 145 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 147

A-CH_2-CH_2-B

The products from Example 146 are reacted according to the procedure of Example 49. This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 148

A-CO-C≡C-B

The bromides from Table 2 (B-Br) are reacted according to the procedure of Example 47A. The resultant acetylenes are reacted according to the procedure of Example 50 with the exception that 4-bromoimidazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). For products derived from halides 202-230 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 149

A-CO-CH=CH-B

The products from Example 148 are reacted according to the procedure of Example 48.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to

prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 150

A-CO-CH_2-CH_2-B

The products from Example 149 are reacted according to the procedure of Example 49.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 151

A-SO_2-B

The anilines from Table 1, entries 28-132 (B-NH_2) are reacted according to the procedures of Example 13A. The resultant fluorides are reacted according to the procedure of Example 13 with the exception that 2-mercaptopyridine is replaced by a mercaptan from Table 7 (A-SH). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from mercaptans 301-394 from Table 7, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 152

A-CH_2SO_2-B

The procedure of Example 12 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1, entries 28-132 (B-NH_2) and 2-chloromethylpyridine hydrochloride is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting

group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

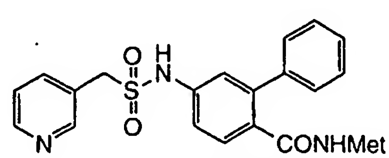
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 153

A-SO_2-CH_2-B

The bromides from Table 2, entries 28-132 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are reacted according to the procedure of Example 37 with the exception that 2-bromothiazole is replaced by a halide from Table 8 (A-Cl, A-Br, or A-I). The resultant sulfides are oxidized according to the procedure of Example 14A. For products derived from halides 202-239 from Table 8, the LiOH hydrolysis step is followed by removal of the tert-butyloxycarbonyl (Boc) amine protecting group by stirring the resultant compound from the LiOH hydrolysis step in a 1:1 mixture of dichloromethane and trifluoroacetic acid until TLC analysis indicates that the reaction is complete. The solvent is evaporated and the residue is purified by chromatography on silica gel.

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 154

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

Example 154A

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine methyl ester

A mixture of 3-chlorosulfonylmethylpyridine hydrochloride (1.0 equivalent) and (4-amino-2-phenylbenzoyl)methionine methyl ester (1.0 equivalent) in dichloromethane is treated with triethylamine (2.2 equivalents). When judged complete by TLC analysis, the reaction is diluted with ethyl acetate, and then is washed with pH 4 water, saturated $NaHCO_3$, and brine. The mixture is dried and concentrated to give the crude title compound which is purified by chromatography on silica gel.

Example 154B

{4-[(3-sulfonylmethylpyridyl)amino]-2-phenylbenzoyl}methionine

The resultant compound from Example 154A is hydrolyzed according to the procedure of Example 1B to give the title product.

Example 155

$A\text{-}CH_2SO_2\text{-}NH\text{-}B$

The procedure of Example 154 is used with the exception that 4-amino-2-phenylbenzoyl methionine methyl ester is replaced by an aniline from Table 1 ($B\text{-}NH_2$) and 3-chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 ($A\text{-}SO_2Cl$).

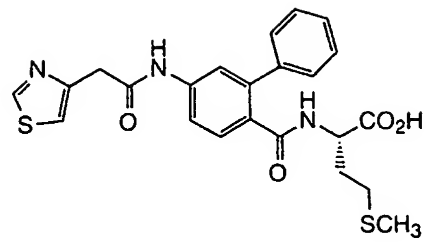
This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the anilines in Table 1 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.

Example 156

$A\text{-}SO_2\text{-}NH\text{-}CH_2\text{-}B$

The bromides from Table 2 (B-Br) are reacted according to the procedures of Example 16F-G. The resultant alcohols are converted to the corresponding amines according to the procedures of Examples 18A-B. These amines are reacted according to the procedure of Example 154 with the exception that -chlorosulfonylmethylpyridine hydrochloride is replaced by a sulfonyl chloride from Table 9 ($A\text{-}SO_2Cl$).

This example also encompasses compounds comprising a C-terminal ester moiety, in which case the final LiOH step is eliminated and the amino acid methyl esters used to prepare the bromides in Table 2 are replaced by the corresponding ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, isoamyl, hexyl, octyl, cyclohexyl or phenethyl esters.



Example 162

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

Example 162A

Thioformamide

To a mechanically-stirred solution of formamide (4.0 mL, 100 mmol) in THF (45 mL) was added P_4S_{10} (4.5 g, 10.1 mmol) while the reaction mixture was maintained at <37 °C using an ice-water bath. The reaction mixture was then stirred for 5.5 hours at ambient temperature. The reaction mixture was filtered through a pad of celite and the filter cake was washed with THF. The filtrate was concentrated and in vacuo and then under high vacuum for 4 hours to give thioformamide which was used without further purification.

Example 162B

Ethyl 4-bromoacetoacetate

To a mechanically-stirred solution of ethyl acetoacetate (59 mL, 463 mmol) in ether (75 mL) was added bromine (23.5 mL, 912 mmol) while the reaction temperature was maintained below 23 °C using an ice-water bath. The yellow-orange solution was stirred for 5 hours with cooling and then was stirred overnight at ambient temperature. Ice (60 g) was added and the reaction mixture was extracted with ether. The organic phase was washed twice with aqueous $NaHCO_3$ saturated with NaCl and once with brine. The ether solution was stirred for 1 day over $CaCl_2$ and then was filtered through celite. The filter cake was rinsed with dichloromethane. The filtrate was concentrated in vacuo to give ethyl 4-bromoacetoacetate (71.5 g) which was stored in the dark and stabilized with $BaCO_3$ (300 mg).

Example 162C

Ethyl 4-Thiazolylacetate

To a solution in absolute ethanol (18 mL) of ethyl 4-bromoacetoacetate (7.0 mL, 10.4 g, 49.7 mmol), prepared as in Example 162B, was added a solution in absolute ethanol/dioxane/toluene of thioformamide (4 g, 65 mmol), prepared as in Example 162A,

while the reaction temperature was maintained below 35 °C using an ice-water bath. The reaction mixture was stirred at reflux for 30 minutes, and then was cooled to ambient temperature. The reaction mixture was poured into aqueous 2N HCl (210 mL) and extracted twice with ether. The organic extracts were discarded and the aqueous phase was taken to ph 7-8 with $NaHCO_3$. The aqueous phase was extracted twice with ether. The ether extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4.7 g of a dark oil. The oil was distilled at 20 mm Hg to give ethyl 4-thiazolylacetate (2.5 g, bp 111-122 °C) as light-yellow oil.

Example 162D

4-Thiazoylacetic acid

A mixture of ethyl 4-thiazolylacetate (2.4 g, 14 mmol), prepared as in Example 162C, and aqueous 10% NaOH was stirred for 10 minutes at ambient temperature. The reaction mixture was cooled to 0 °C and taken to pH 2-3 with concentrated HCl. The resulting white solid was filtered, washed with water and dried under high vacuum in the presence of P_2O_5 to give 4-thiazoylacetic acid (905 mg).

Example 162E

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

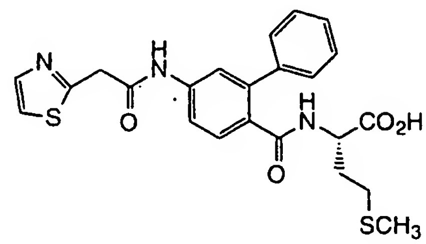
To a suspension in dichloromethane (10 mL) of 4-thiazolylacetic acid (460 mg, 3.22 mmol), prepared as in Example 162D was added oxalyl chloride (300 μL, 3.44 mmol) and DMF (5 mL). The mixture was stirred for 1.5 hours after bubbling ceased, and then was added over 5 minutes to a 5 °C 2-phase mixture of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 1.2 g, 3.2 mmol) in diclhloromethane (12 mL) and saturated aqueous $NaHCO_3$ (15 mL). The cold bath was removed and the reaction mixture was stirred for 1.5 hours. The reaction mixture was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a dark-brown residue (1.0 g). Chromatography on silica gel (10% ethyl acetate hexane) gave [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (581 mg) as a light-yellow powder.

Example 162F

[4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazo-4-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 162E, using lithium hydroxide hydrate according to the method of Example 159. ^1H NMR (300 MHz, DMSO-d6) δ 10.42 (s, 1H), 9.06 (d, 1H), 8.43 (d, 1H), 7.70 (d, 1H), 7.63

(dd, 1H), 7.52 (d, 1H), 7.40 (d, 1H), 7.35 (m, 5H), 4.28 (m, 1H), 3.90 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH_3) m/e 470 $(M+H)^+$. Anal calcd for $C_{23}H_{23}N_3O_4S_2$: C, 58.83; H, 4.94; N, 8.95. Found: C, 58.44; H, 4.87; N, 8.58.



Example 163

[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

Example 163A

3-bromosuccinaldehydic acid ethyl ester

To a 0-5 °C mechanically-stirred solution in diethyl ether (100 mL) of succinaldehydic acid ethyl ester (10.0 g, 77 mmol) was added bromine (3:9 g, 151 mmol) over 2.5 hours. The reaction mixture was stirred for an additional 1.25 hours and the ether was distilled at atmospheric pressure. The remaining yellow oil was distilled (6.0-6.5 mm Hg, bp 95-101 °C) to give 3-bromosuccinaldehydic acid ethyl ester (10.7 g, 66%).

Example 163B

Ethyl 2-thiazolyl acetate

To a slurry of thioformamide (3.9 g, 64 mmol) in diethyl ether (40 mL) and tetrahydrofuran (15 mL) was added 3-bromo-succinaldehydic acid ethyl ester (10.6 g, 51 mmol), prepared as in Example 163A. The reaction mixture was heated at reflux for 30 minutes, then ethanol (50 mL) was added, 30-40 mL of ether was distilled off, and the reaction mixture was heated at reflux for one hour. The reaction mixture was cooled to ambient temperature and aqueous 2N HCl (200 mL) was added. The mixture was extracted twice with ether. The aqueous phase was taken to pH 7-8 with $NaHCO_3$ (40 g) and was extracted with ether and twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give an orange oil which was purified by distillation (3 mm Hg, bp 109-111 °C) to give ethyl 2-thiazolyl acetate (2.15 g).

Example 163C

2-Thiazolyl acetic acid

Ethyl 2-thiazolyl acetate (2.35 g, 13.7 mmol), prepared as in Example 163B, was added to 10% aqueous KOH. After about 10 minutes all of the oil dissolved to give a clear, bright-yellow solution. The reaction mixture was cooled to 0 °C and the pH was adjusted to 2-3 using concentrated HCl. The resulting solids were filtered off, rinsed with water, and dried over P_2O_5 under high vacuum to give 2-thiazolyl acetic acid (1.44 g).

Example 163D

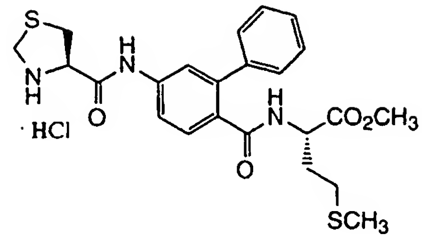
[4-(thiazo-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution in DMF (4 mL) of 2-thiazolyl acetic acid (300 mg, 2.1 mmol), prepared as in Example 163C, was added 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (373 mg, 2.3 mmol) followed by ethyl dimethylaminopropyl carbodiimide hydrochloride (442 mg, 2.3 mmol), and a solution of 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8, 760 mg, 2.0 mmol) in dichloromethane (3 mL) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and washed saturated aqueous $NaHCO_3$ (2x) and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to give a brown solid (1.12 g). Chromatography on silica gel (ethyl acetate) gave [4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (600 mg).

Example 163E

[4-(thiazol-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of [4-(thiazo-2-ylmethylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 163D) using the procedure of Example 159. ^1H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.00 (d, 1H), 8.45 (d, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.61 (dd, 1H), 7.42 (d, 1H), 7.38 (m, 5H), 4.28 (m, 1H), 4.01 (s, 2H), 2.25 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H); MS (DCI-NH_3) m/e 470 $(M+H)^+$. Anal calcd for $C_{23}H_{23}N_3O_4S_2 \cdot H_2O$: C, 56.66; H, 517; N, 8.62. Found: C, 56.75; H, 4.96; N, 8.45.



Example 164

[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

Example 164A

N-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid

To a solution of (R)-(-)-thiazolidine-4-carboxylic acid (1.0 g, 7.5 mmol) in aqueous 1N NaOH (9 mL) and THF (9 mL) was added a solution of di-*tert*-butyldicarbonate (1.62 g, 7.4 mmol) in THF (9 mL). An additional 2 mL of aqueous NaOH was added and the reaction mixture was stirred overnight at ambient temperature. Additional aqueous NaOH was added to make a clear solution and the reaction mixture was washed with hexanes (3x). The hexane extracts were washed twice with saturated aqueous $NaHCO_3$. The combined aqueous layers were acidified to pH 2 with 1.1 M $NaHSO_4$ and extracted twice with ether. The combined ether layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to give *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid (1.3 g) which was used without further purification.

Example 164B

[4-(*N-tert*-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester

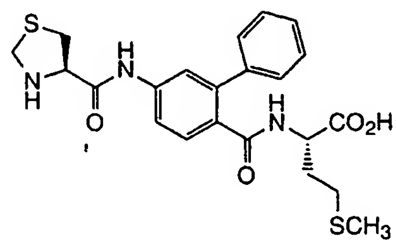
The desired compound was prepared by coupling of *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid, prepared as in Example 164A with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8) according to the method of Example 163D.

Example 164C

[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride

To a mixture of [4-(*N-tert*-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester (270 mg, 0.47 mmol) and thiophenol (0.1 mL, 0.97 mmol) was added 4N HCl-dioxane (10 mL) and the reaction mixture was stirred for 45

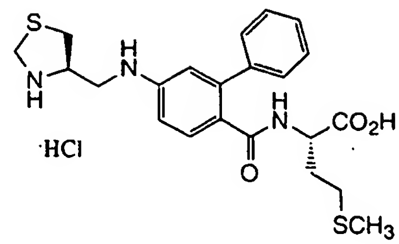
minutes at ambient temperature. The reaction mixture was partitioned between water and ether. The aqueous phase was extracted with ether. The organic extracts were discarded and the aqueous phase was lyophilized to give [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (150 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.53 (s, 1H), 8.45 (d, 1H), 7.68 (m, 2H), 7.42 (dd, 1H), 7.37 (m, 5H), 4.27 (m, 4H), 3.70, 3.25, 3.12 (all m, total 3H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 474 $(M+H)^+$. Anal calcd for $C_{23}H_{28}ClN_3O_4S_2 \cdot 1.4H_2O$: C, 51.61; H, 5.80; N, 7.85. Found: C, 51.67; H, 5.55; N, 7.28.



Example 165

[4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine

To a 0 °C solution in methanol (4.3 mL) of [4-((R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (75 mg, 0.15 mmol) was added a solution of lithium hydroxide hydrate (18 mg, 0.43 mmol) in water (0.5 mL). The reaction mixture was stirred for 1.5 hours, then the cold bath was removed and stirring was continued overnight at ambient temperature. The reaction mixture was concentrated in vacuo and aqueous 2N HCl was added to the residue. The cloudy solution was extracted with ethyl acetate and chloroform-isopropanol. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 4[-((R)-thiazolidine-4-carbonyl)amino-2-phenylbenzoyl]methionine (67 mg). ^{1}H NMR (300 MHz, DMSO-d_6) δ11.10 (s, 1H), 8.60 (d, 1H), 7.70 (s, 1H), 7.68 (dd, 1H), 7.44 (dd, 1H), 7.37 (m, 5H), 4.63 (m, 1H), 4.37 (m, 3H), 3.70 (m, 1H), 3.63 (s, 3H), 3.40 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 460 $(M+H)^+$. Anal calcd for $C_{22}H_{25}N_3O_4S_2 \cdot 0.8$ HCl: C, 54.06; H, 5.32; N, 8.60. Found: C, 54.21; H, 5.34; N, 8.00.



Example 166

[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

Example 166A

N-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide

To a solution in DMF (10 mL) of *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid (777 mg, 3.33 mmol), prepared as in Example 164A, 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (602 mg, 3.69 mmol), and ethyl dimethylaminopropyl carbodiimide hydrochloride (709 mg, 3.70 mmol) was added *N,O*-dimethylhydroxylamine hydrochloride (357 mg, 3.66 mmol) and 4-methylmorpholine (0.44 mL, 4.01 mmol) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with ethyl acetate and extracted with aqueous 1M H3PO4 (2x), saturated aqueous NaHCO3 (2x), and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Chromatography on silica gel (2:1 hexane-ethyl acetate) gave *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (605 mg) as a thick yellow oil.

Example 166B

N-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde

To a -78 °C solution in THF (6 mL) of *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxylic acid-*N*-methoxy-*N*-methyl amide (550 mg, 2.0 mmol) was added lithium aluminum hydride (1.0 M in THF, 3.0 mL, 3.0 mmol) and the reaction mixture was stirred for 2.5 hours. The reaction was quenched with 10% aqueous citric acid (30 mL) and warmed to ambient temperature. The mixture was warmed to ambient temperature and extracted with ether (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give *N-tert*-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde (440 mg) which was used without further purification.

Example 166C

[4-(*N-tert*-butoxycarbonyl-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

N-tert-butoxycarbonyl-(R)-(-)thiazolidine-4-carboxaldehyde was reductively aminated with 4-amino-2-phenylbenzoyl methionine methyl ester (compound 8) according to the procedure of Example 158B.

Example 166C

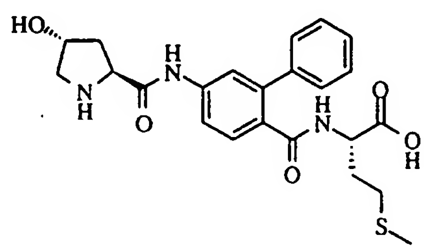
[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared according to the method of Example 164C, except substituting [4-(*N-tert*-butoxycarbonyl-(R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166B, for [4-(*N-tert*-butoxycarbonyl-(R)-thiazolidin-4-ylcarbonyl)amino-2-phenylbenzoyl]methionine methyl ester.

Example 166D

[4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

The desired compound was prepared by saponification of [4-((R)-thiazolidin-4-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 166C according to the procedure of Example 165. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.03 (d, 1H), 7.33 (m, 6H), 6.69 (dd, 1H), 6.59 (d, 1H), 4.30 (dd, 2H), 4.23 (m, 1H), 3.86 (m, 1H), 3.46 (dd, 2H), 3.22 (dd, 1H), 2.91 (m, 1H), 2.24 (m, 2H), 2.00 (s, 3H), 1.85 (m, 2H); MS (APCI) m/e 446 $(M+H)^+$, 444 $(M-H)^-$. Anal calcd for $C_{22}H_{27}N_3O_3S_2{\cdot}HCl{\cdot}0.25H_2O$: C, 54.31; H, 5.90; N, 8.64. Found: C, 54.20; H, 6.07; N, 8.35.



Example 169

[4-(4-hydroxy-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

Example 169A

N-Boc-4-(t-butyldimetylsilyl)hydroxyproline

To a solution of 1.3 g (3.6 mmol) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline methyl ester, prepared as described by Rosen et al., *J. Med. Chem.* **1988**, *31*, 1598, in 10 ml of methanol was added 5 ml (5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 1.05 g (96 %) of *N*-Boc-4-(*t*-butyldimethylsilyl-oxy)proline as a foamy solid which was used without further purification.

Example 169B

{4-[N-Boc-4-(t-butyldimethylsilyloxy)prolinyl]amino-2-phenylbenzoyl}methionine methyl ester

To a solution in dichloromethane (15 mL) of *N*-Boc-4-(*t*-butyldimethylsilyloxy)proline (1.0 g, 3.29 mmol), prepared as in Example 169A, was added 550 μ l(3.9 mmol) of triethylamine in an ice bath under argon, followed by 470 μ l(3.6 mmol) of isobutyl chlroformate. The reaction mixture was stirred for 40 minutes. At this time TLC showed the absence of the starting material. To this solution, 1.07 g (2.97 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) in 10 ml of dichloromethane was introduced. The reaction mixture was stirred overnight, during which time the ice bath expired. The reaction mixture was washed with 1 N HCl, 5 % sodium bicarbonate, and water, dried over magnesiun sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (7:3 hexanes-ethyl acetate) to yield 1.92 g (94 %) of {4-[*N*-Boc-4-(*t*-butyldimetylsilyl)hydroxyprolinyl]-2-phenylaminobenzoyl}methionine methyl ester as a foamy solid. mp 83 ^{O}C; $[\alpha]^{25}_{D}$ -36.2 (*c*=0.63, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, *J*=6 0Hz), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for $C_{35}H_{51}N_3O_7SSi$: 685.9498, found: 685.3217.

Example 169C

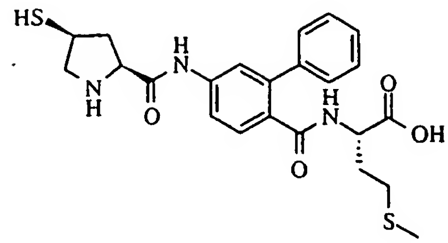
[4-(N-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 1.82 g (2.65 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169B, in 20 ml of THF was added 3 ml (3 mmol) of 1 M tetra-*n*-butylammoniun floride in THF. The reaction mixture was stirred overnight, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 864 mg (57 %) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester as a white solid: mp 121-123 ^{o}C; $[\alpha]^{25}_{D}$ -53.3 (*c*=0.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for $C_{29}H_{37}N_3O_7S$: 571.6872, found: 571.2352.

Example 169D

[4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 358 mg (0.62 mmol) of [4-(*N*-Boc-4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 169C, in 6 ml of methanol was added 1 ml (1 mmol) of 1 N LiOH in an ice bath and the reaction mixture was stirred for 4 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between chloroform and water and extracted 3 times with chloroform. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 317 mg (92 %) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added 306 mg (0.54 mmol) of the acid. After 3 hours, the reaction mixture was thoroughtly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 254 mg (72%) of [4-(4-hydroxyprolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 90 % (purity); mp 127 (sub.), 154-157 ^{o}C (dec.); ^1H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (CD_3OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



Example 170

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine·trifluoroacetate

Example 170A

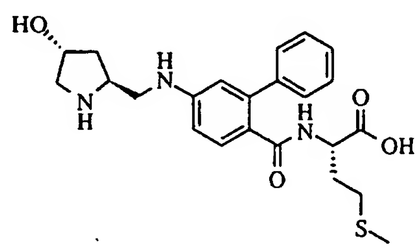
[4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of 140 mg (0.22 mmol) of {4-[*N*-Boc-4-(*t*-butyldimethylsilyloxy)-prolinyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 169C, in 10 ml of THF was added 128 mg (0.48 mmol) of triphenylphosphine, followed by 96 µl(0.49 mmol) of diisopropyl azodicarboxylate at 0 ^{o}C under argon atmosphere. The reaction mixture was stirred for 40 minutes and 35 µl (0.49 mmol) of thiolacetic acid was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel (3:1 hexanes-ethyl acetate) to yield 123 mg (89 %) of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-s-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 97 ^{o}C; $[\alpha]^{25}_{D}$ -105.2 (*c*=0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.68-7.38 (m, 8H), 6.37 (s, 1H), 4.58 (br s, 4H), 4.02 (m, 1H), 3.64 (s, 3H), 3.33 (br s, 1H), 2.52 (br s, 1H), 2.30 (s, 3H), 2.03 (t, 2H, *J*=7.8Hz), 1.99 (s, 3H), 1.90 (m, 1H), 1.74 (m, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 195.5, 172.2, 169.9, 169.3, 169.0, 155.3, 140.3, 140.0, 130.2, 129.2, 128.7, 128.4, 127.7, 120.6, 117.9, 81.6, 60.2, 53.2, 52.3, 51.9, 39.3, 34.0, 31.2, 30.5, 29.6, 28.3, 15.2; MS (EI) *m/z* (relative intensity) 629 (M^{+}, 6), 571 (25), 529 (45), 196 (100).

Example 170B

[4-((2S,4S)-4-mercaptopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate

To a solution of 120 mg (0.19 mmol) of [4-((2S,4S)-1-Boc-4-acetylthiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 170A, in 5 ml of THF was added 1 ml (1 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned between dichloromethane and water and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 105 mg (94 %) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine as a white solid. To 5 ml of a 1:1 solution of TFA and dichloromethane were added 105 mg (0.17 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, the reaction mixture was thoroughtly evaporated in high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 90 mg (80%) of [4-((2S,4S)-4-thiopyrrolidin-2-carboxy)amino-2-phenylbenzoyl]methionine trifluoroacetate: HPLC 86 % (purity); mp 169 ^{o}C (dec.); ^{1}H NMR (300 MHz, CD_3OD) δ 7.59-7.28 (m, 8H), 4.39 (m, 2H), 3.53 (m, 1H), 3.38 (m, 1H), 3.22-3.12 (m, 2H), 2.87 (m, 1H), 2.12 (m, 1H), 2.00-1.92 (m, 5H), 1.72 (m, 1H); ^{13}C NMR (CD_3OD) δ 175.0, 172.7, 167.5, 142.6, 140.7, 133.4, 130.2, 129.8, 129.7, 129.0, 122.5, 119.5, 61.8, 55.3, 53.2, 41.1, 36.2, 31.6, 31.1, 15.3.



Example 171

[4-((2S,4R)-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

Example 171A

(2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyloxy]-2-(hydroxymethyl)pyrrolidine

A suspension of calcium chloride (780 mg, 7 mmol) and 530 mg (14 mmol) of sodium borohydride in 25 ml of THF was stirred at ambient temperature for 5 hours. To this suspension was added 2.5 g (7 mmol) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyl)oxy]-2-(carbomethoxy)pyrrolidine methyl ester in 5 ml of THF and the reaction mixture was stirred overnight. Excess hydride was destroyed by adding hydrated sodium sulfate. The white

precipitate was removed by suction filtration through a pad of Celite, and the filtrate was dried over magnesium sulfate and concentrated to give 2.25 g (97 %) of (2S,4R)-1-Boc-4-[(*t*-butyldimethylsilyl)oxy]-2-(hydroxymethyl)pyrrolidine as an colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6H), 0.85 (s, 9H), 1.47 (s, 9H), 1.90 (m, 1H), 3.27-4.25 (complex m, 7H), 4.89 (br d, 1H, J=6.6 Hz): MS (EI) *m/z* 332 (M^+), 258.

Example 171B

(2S,4R)-1-Boc-4-[t-butyldimethylsilyloxy]pyrrolidin-2-aldehyde

To a solution of 1 ml (14.1 mmol) of DMSO in 7 ml of dichloromethane were added 1.48 ml (10.4 mmol) of trifluoroacetic anhydride in 3.5 ml of dichloromethane at -78 ^oC under a slight stream of argon. After 10 min, 2.35 g (7 mmol) of (2S,4R)-1-Boc-4-[*t*-butyldimethylsilyloxy]-2-(hydroxymethyl)pyrrolidine, prepared as in Example 171A, in 7 ml of dichloromethane was added to this mixture at the same temperature. The reaction mixture was stirred for 1 hour. To this solution was added 3 ml (21.5 mmol) of triethylamine. The reaction mixture was stirred for 1 hour at -78 ^oC, slowly warmed to room temperature, and concentrated. The residue was chromatographed on silica gel (9:1 hexanes-ethyl acetate to yield 1.08 g (47 %) of (2S,4R)-1-Boc-4-[t-butyldimethylsilyloxy]-pyrrolidin-2-aldehyde as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1H), 4.33 (m, 1H), 4.17 (m, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 1.93 (m, 2H), 1.41 (s, 9H), 0.82 (s, 9H), 0.07 (s, 6H).

Example 171C

{4-[(2S,4R)-1-Boc-4-*t*-butyldimethylsilyloxy]pyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl}methionine methyl ester

To a solution of 0.75 g (2.09 mmol) of [2-phenyl-4-aminobenzoyl]methionine methyl ester (compound 8) and 0.7 g (2.1 mmol) of (2S,4R)-1-Boc-4-[t-butyldimethylsilyloxy]-pyrrolidin-2-aldehyde, prepared as in Example 171B, in 10 ml of methanol were added 1 ml of acetic acid, followed by 0.2 g (3.1 mmol) of sodium cyanoborohydride. The reaction mixture was stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5 % sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesiun sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel (2:1 hexanes-ethyl acetate) to yield 261 mg (74 %) of {4-[(2S,4R)-1-Boc-4-(*t*-butyldimetylsilyl)oxypyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester as a white solid: mp 48 ^oC; $[\alpha]^{25}_D$ -15.6 (c=1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J=8.5 Hz), 7.37 (m, 6H), 6.57 (1, 1H), 6.37 (s, 1H), 5.60 (br s, 2H), 4.60 (m, 1H), 4.31 (m, 2H), 3.77 (s, 3H), 3.61-3.10 (m, 5H), 2.06 (t, 2H, J=8.2 Hz), 1.98 (s, 3H), 1.85 (m, 1H), 1.60 (m, 1H), 1.43 (s, 9H);

0.84 (s, 9H), 0.03 (s, 6H); HRMS (EI) calculated for $C_{35}H_{53}N_3O_6SSi$: 671.3424, found: 671.3424.

Example 171D

[4-((2S,4R)-N-Boc-4-hydroxylpyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester

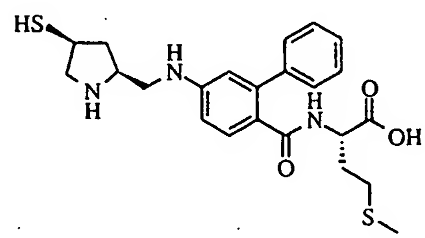
To a solution of 770 mg (1.14 mmol) of {4-[(2S,4R)-1-Boc-4-(*t*-butyldimethylsilyloxy)-pyrrolidin-2-ylmethyl]amino-2-phenylbenzoyl}methionine methyl ester, prepared as in Example 171C, in 10 ml of THF was added 2 ml (2 mmol) of 1 M tetra-*n*-butylammoniun fluoride in THF. The reaction mixture was stirred for 15 minutes at ambient temperature, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to obtain 467 mg (73 %) of 2-[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester as a foamy solid: mp 81 ^{o}C; $[\alpha]^{24}_{D}$ -15.9 (c=0.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J=9.0 Hz), 7.35 (m, 6H), 6.57 (br s, 1H), 6.38 (br s, 1H), 5.67 (d, 1H, J=7.6 Hz), 5.54 (br s, 1H), 4.55 (m, 1H), 4.09 (m, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.71 (br s, 1H), 2.04(m, 2H), 1.96 (s, 3H), 1.80 (m, 1H), 1.60 (m, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.0, 168.5, 156.4, 150.0, 141.7, 141.1, 131.3, 128.6, 127.7, 121.8, 113.5, 110.8, 80.2, 69.5, 69.1, 60.3, 55.3, 54.8, 52.2, 51.7, 49.0, 38.6, 31.5, 29.4, 28.3, 25.5, 15.2; HRMS (EI) calculated for $C_{29}H_{39}N_3O_6S$: 557.2559, found: 557.2559.

Example 171E

[4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride

To a solution of 125mg (0.22 mmol) of [4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 171D, in 5 ml of THF was added 0.5 ml (0.5 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 5 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 50 mg (42 %) of the resulting free acid as a solid. To a 2 ml of 1:1 solution of TFA and dichloromethane was added 50 mg (0.09 mmol) of the acid. After 30 minutes, the reaction mixture was thoroughtly evaporated in high vacuum to

give an oily residue. The residue was triturated with 0.3 ml of 3 M anhydrous HCl-ether in 5 ml of ether and the white solid was collected by filtration to give 35 mg (74 %) of [4-((2S,4R)-N-Boc-4-hydroxypyrrolidin-2-ylmethyl)amino-2-phenylbenzoyl]methionine hydrochloride: HPLC 72 % (purity). ^{1}H NMR (300 MHz, CD_3OD) δ 7.71-7.30 (m, 6H), 6.76 (dd, 1H, *J*= 8.4, 2.4 Hz), 6.69 (d, 1H, *J*= 2.2 Hz), 4.55 (d, 1H, *J*= 4.0 Hz), 4.44 (dd, 1H, *J*= 9.3, 4.2 Hz), 4.12 (m, 1H), 3.62-3.19 (m, 4H), 2.02 (s, 3H), 2.21-1.75 (m, 6H).



Example 172

[4-((2S,4S)-4-thiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

Example 172A

[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester and

[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenyl)benzoyl]methionine methyl ester

To a solution of 153 mg (0.27 mmol) of 2-Phenyl-4-[(2S,4R)-N-Boc-4-hydroxy]pyrrolidine-2-methyl]aminobenzoylmethionine methyl ester, prepared as in Example 171D, in 10 ml of THF were added 142 mg (0.54 mmol) of triphenylphosphine, followed by 107 *ul* (0.54 mmol) of diisopropyl azodicarboxylate at 0 °C under argon atmosphere. The mixture was stirred for 30 minutes and 40 *ul* (0.56 mmol) of thiolacetic acid was added at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude products were chromatographed on silica gel (1:1 hexanes-ethyl acetate) to give 106 mg (63 %) of [4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester and 35 mg (24 %) of the bicyclic [4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenyl)benzoyl]methionine methyl ester as white solids.

[4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2-yl-methylamino)-2-phenylbenzoyl]methionine methyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, J=8.4 Hz), 7.37 (m, 6H), 6.60 (br s, 1H), 6.41 (br s, 1H), 5.66 (d, 1H, J=7.8 Hz), 5.53 (br s, 1H), 4.58 (m, 1H), 4.23 (br s, 1H), 4.02 (br s, 1H), 3.87 (m, 1H), 3.60 (s, 3H), 3.38-3.12 (br s, 2H), 3.12 (dd, 1H, J=6.7, 11.4 Hz), 2.52 (m, 1H), 2.30 (s, 3H), 2.05 (t, 2H, J=7.6 Hz),), 1.97 (s, 3H), 1.82 (m, 1H), 1.62 (m, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 195.0, 172.1, 168.5, 155.8, 150.0, 141.8, 141.4, 131.5, 128.8, 128.6, 127.8, 122.2, 113.7, 111.0, 80.7, 60.4, 56.5, 52.3, 51.8, 49.2, 39.3, 36.0, 31.7, 30.6, 29.6, 28.4, 15.3; HRMS (EI) calculated for $C_{31}H_{41}N_3O_6S_2$: 615.2436, found: 615.2436.

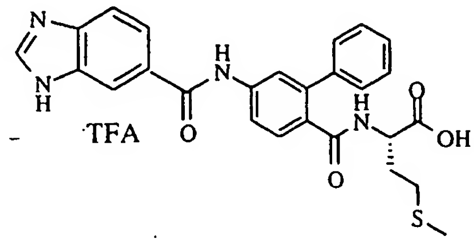
[4-((2S,5S)-4-Boc-1,4-diazabicyclo(2,2,1)octan-1-yl)-2-phenyl)benzoyl]methionine methyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 1H, J=8.6 Hz), 7.54-7.40 (m, 6H), 6.57 (d, 1H, J=9.0 Hz), 6.36 (s, 1H), 5.68 (br s, 1H), 4.63 (m, 2H), 4.42 (br s, 1H), 3.63 (s, 3H), 3.58-3.17 (m, 5H), 2.10 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.66 (m, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.2, 168.5, 154.2, 148.7, 142.0, 141.4, 132.1, 131.7, 129.0, 128.8, 128.1, 122.1, 113.7, 111.2, 80.0, 57.4, 56.4, 52.5, 52.0, 37.9, 37.4, 31.9, 29.7, 28.7, 15.5; HRMS (EI) calculated for $C_{29}H_{37}N_3O_5S$: 539.2454, found: 539.2453.

Example 172B

[4-((2S,4S)-4-thiopyrrolidin-2yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride

To a solution of 86 mg (0.14 mmol) of [4-((2S,4S)-N-Boc-4-acetylthiopyrrolidin-2yl-methylamino)-2-phenylbenzoyl]methionine methyl ester in 2 ml of THF was added 0.4 ml (0.4 mmol) of 1 N LiOH in an ice bath. The reaction mixture was stirred for 2 hours. The reaction mixture was adjusted to pH 2-3 with 1 N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned between dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1 N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give 67 mg (85 %) of the resulting free acid as a white solid. To 2 ml of 1:1 solution of TFA and dichloromethane were added 67 mg (0.12 mmol) of the acid, followed by a few drops of triethylsilane. After 30 minutes, The reaction mixture was thoroughtly evaporated under high vacuum to give an oily residue. The residue was triturated with anhydrous ether and the white solid was collected by filtration to give 62 mg (97 %) of [4-((2S,4S)-4-thiopyrrolidin-2yl-methylamino)-2-phenylbenzoyl]methionine hydrochloride: HPLC 83% (purity); ^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.35 (m, 6H), 6.76 (d, 1H, J=8.4 Hz), 6.70 (s, 1H), 4.45 (m, 1H), 3.91 (m, 1H), 3.68-3.30 (m, 5H), 3.15 (m, 1H), 2.66 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 2.01 (s, 3H), 1.79 (m, 2H); ^{13}C NMR

(CD3OD) δ 175.0, 173.3, 150.5, 143.5, 142.3, 131.3, 129.9, 129.6, 128.7, 125.9, 115.9, 112.5, 60.9, 54.6, 53.3, 45.8, 40.3, 35.4, 31.8, 31.0, 15.3.



Example 182

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

Example 182A

(1H-1-*p*-Toluenesulfonylbenzimidazol-5-yl)carboxylic acid

5-Benzimidazolecarboxylic acid (1.0 g, 6.2 mmol) and *p*-toluenesulfonyl chloride (1.2 g, 6.2 mmol) were suspended in 10 mL of distilled water. Aqueous 1N sodium hydroxide was added periodically to maintain a pH of approximately 9 over a period of 4 hours. The reaction mixture was washed with methylene chloride (3X50 mL.) and was adjusted to pH 3 with 1N hydrochloric acid. The precipitate which formed was collected by vacuum filtration, washed with distilled water and hexanes and air dried to give (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.75 g, 38%) as a white solid.

Example 182B

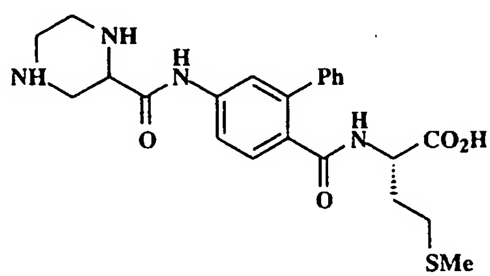
[4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

To 50 mL of methylene chloride containing [4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (compound 8, 0.65 g, 1.64 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 0.34 g, 1.8 mmol) was added (1H-1-*p*-toluenesulfonylbenzimidazol-5-yl)carboxylic acid (0.52 g, 1.64 mmol), prepared as in Example 182A, and the mixture was cooled to 0°C. Triethylamine (0.16 g, 1.64 mmol) was slowly added to the stirred solution. After 1 hour, the ice bath was removed and the reaction was stirred for an additional 96 hours. The organic layer was washed with distilled water, dried over magnesium sulfate and concentrated. The residue was purified by flash column chromatography (4:1 ethyl acetate/hexanes) to give [4-(1H-1-*p*-toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.63 g, 59%) as a white solid.

Example 182C

[4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate

[4-(1H-1-*p*-Toluenesulfonylbenzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.2 g, 0.3 mmol), prepared as in Example 182B, was added to 5 mL of tetrahydrofuran (THF) and the mixture was cooled to 0°C. Lithium hydroxide (5 mL., 0.5M) was slowly added and the reaction mixture was stirred for 2 hours. The THF was removed by evaporation and 0.5M HCl was added to adjust the pH to between 2 and 3 and the precipitate which formed was collected by vacuum filtration. The solid was purified by reverse phase preparative HPLC (Waters 25X10 cm, C-18 column, 220 nm UV detector, flow rate 15 mL./min, linear gradient from 5% acetonitrile and 95% water containing 0.1% TFA to 60% acetonitrile in 40 minutes) and pure fractions were pooled and lyophilized to give [4-(1H-benzimidazol-5-ylcarboxyamino)-2-phenylbenzoyl]methionine trifluoroacetate as a white solid (0.146 g, 87%). ^{1}H NMR (300 MHz, DMSO-d6) δ 10.56 (s, 1H), 9.05 (s, 1H), 8.47 (d, 1H, *J*= 7.8 Hz), 8.40 (s, 1H), 8.04 (d, 1H, *J*= 8.1 Hz), 7.88-7.89 (m, 2H), 7.33-7.48 (m, 6H), 4.30 (m, 1H), 2.16-2.29 (m, 2H), 2.06 (s, 3H), 1.84-2.00 (m, 2H). MS m/e 489 $(M+H)^+$.



Example 185

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.

Example 185A

di-*tert*-butoxycarbonylpiperidine-2-carboxylic acid

Di-*tert*-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then concentrated under reduced pressure to remove THF. The residue was saturated with solid $NaHCO_3$ and extracted with ether (2 x 30 mL). The aqueous layer was cooled to 0 °C and then adjusted to pH = 3 with 2 M aqueous HCl. A precipitate developed. The mixture was

extracted with CH_2Cl_2 (3 x 75 mL), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 7.61 g (98%) of di-*tert*-butoxycarbonylpiperidine-2-carboxylic acid as a tan solid. ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 18 H), 2.80-2.98 (br, 1 H), 3.04-3.36 (br comp, 2 H), 3.70-3.83 (br, 1 H), 3.94-4.05 (br, 1 H), 4.44-4.65 (br comp, 2 H), 4.80-4.95 (br, 1 H). LRMS (CI): 292, 331 $(M+1)^+$, 348 $(M+NH_4)^+$.

Example 185B

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester.

The desired compound was prepared by coupling di-*tert*-butoxycarbonylpiperidine-2-carboxylic acid with [4-amino-2-phenylbenzoyl]methionine methyl ester (compound 8) according to the procedure of Example 184A.

Example 185C

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine.

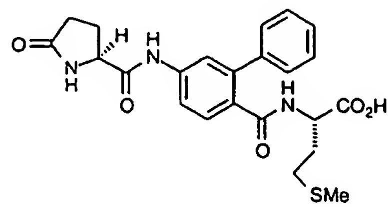
Lithium hydroxide hydrate (0.411 g, 9.60 mmol) was added to a solution of [4-(di-*tert*-butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine methyl ester (*ca* 0.8 g, 1.20 mmol), prepared in Example 185B, in THF/H_2O (4:1, 12 mL). The solution was stirred for 20 hours and then treated with 1 M aqueous HCl (10 mL). The mixture was extracted with ethyl acetate (5 x 10 mL), and the organic extracts were rinsed with 1:1 brine/1 N HCl (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to provide [4-(di-*tert*-butoxycarbonylpiperidin-2-yl)carboxyamino-2-phenylmethionine (0.72 g) as a white foam (est. 89%). ^{1}H NMR (CD_3OD) δ 1.3-1.5 (br, 18 H), 1.7-1.9 (br comp, 2 H), 2.0 (br s, 3 H), 2.1-2.3 (br comp, 2 H), 2.9-4.8 (br comp, 8 H), 7.3-7.5 (br comp, 6 H), 7.5-7.6 (br m, 1 H), 7.6-7.7 (br m, 1 H). LRMS (CI): 657 $(M+1)^+$, 457, 330.

Example 185D

[4-(piperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine hydrochloride.

[4-(di-*tert*-butoxycarbonylpiperidin-2-ylcarboxyamino)-2-phenylbenzoyl]methionine (0.72 g, 1.07 mmol), prepared in Example 185C, was treated with HCl (9.6 mL of a 4 M solution in dioxane, 38.5 mmol) and the solution was stirred for 5 minutes, at which time a pink precipitate was observed. The mixture was treated with pentane (10 mL) and the precipitate was isolated by filtration to afford [4-(piperidin-2-yl)carboxyamino-2-phenylbenzoyl]methionine hydrochloride (0.448 g, 86%). ^{1}H NMR (CD_3OD) δ 1.73-1.88 (m, 1 H), 1.93-2.05 (comp, 4 H), 2.05-2.14 (m, 1 H), 2.14-2.26 (m, 1 H), 3.32-3.64

(comp, 5 H), 3.68-3.85 (comp, 2 H), 3.97 (dd, 1 H), 4.13 (dd, 1 H), 4.73 (dd, 1 H), 7.35-7.50 (comp, 5 H), 7.51-7.59 (m, 1 H), 7.74-7.80 (m, 1 H). LRMS (CI): 457 $(M+1)^+$.



Example 202

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoylmethionine

Example 202A

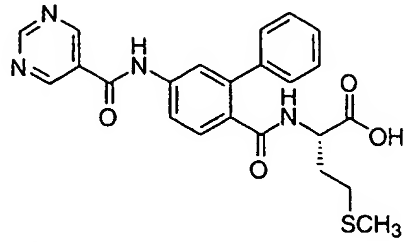
[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of L-pyroglutamic acid (49mg, 0.38 mmol) in 5 mL of DMF was added 3-hydroxy1,2,3-benzotriazin-4(3*H*)-one (62mg, 0.38 mmol), (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (58mg, 0.30 mmol) and [4-amino-2-phenylbenzoyl-L-methionine methyl ester (90mg, 0.38 mmol), prepared as in Example 192B, and the reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was taken up in ethyl acetate and washed with 10 mL 1N HCl, 5 mL satd aqueous $NaHCO_3$ and brine (3 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. Purification by radial chromatography (2-5% methanol-ethyl acetate gradient) to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester (92mg, 79%) as a white solid.

Example 202B

[4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine

LiOH monohydrate (29mg, 0.69 mmol) was dissolved in 1 mL H_2O and added to a solution of [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester, prepared as in Example 202A, (108mg, 0.23 mmol) in 3 mL of THF and the reaction mixture was stirred at 25 °C for 1 hour. The reaction mixture was evaporated and 2 mL of 1N HCl was added to the aqueous residue. The resulting precipitate was filtered and dried under vacuum to give [4-(2-pyrrolidinone-5-ylcarbonylamino)-2-phenylbenzoyl]methionine (96 mg, 91%). ^{1}H NMR (300 mHz, CD_3OD) δ 7.70 - 7.60 (m, 3H), 7.45 - 7.30 (m, 5H), 4.40 (bs, 1H), 2.60 - 2.10 (m, 7H), 2.00 (s, 3H), 1.90 - 1.80 (m, 2H).CIMS MH^+ 456.



Example 219

[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

Example 219A

5-pyrimidinecarboxylic acid methyl ester

A mixture of 5-bromopyrimidine (1.59 g, 10 mmol), 1-propanol (1.5 mL, 20 mmol), bis(triphenylphosphine)palladium(II) chloride (400 mg, 0.50 mmol) and tributylamine (3.72 g, 20 mmol) in DMF was stirred at 90 °C under a carbon monoxide balloon for 10 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with potassium dihydrogenphosphate (1.0 M, 20 mL, twice), water, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50:50:10 hexane-dichloromethane-ether) to give 3-pyrimidinecarboxylic acid methyl ester (715 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1H), 9.30 (s, 2H), 4.36 (t, 2H), 1.83 (sextet, 2H), 1.05 (t, 3H).

Example 219B

[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

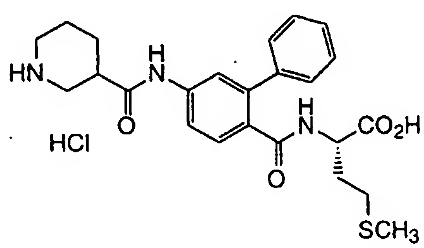
A mixture of the 5-pyrimidinecarboxylic acid methyl ester prepared in Example 219A (682 mg, 4.94 mmol) and aqueous sodium hydroxide solution (4.0 M, 2.5 mL) in THF was heated at 60 °C for 1.5 hours. Hydrochloric acid (6.0 N, 2 mL) was added to the reaction mixture, and the solvent was evaporated *in vacuo*. The residue was dried under high vacuum at 50 °C for 1 hour, and the redesolved in to THF. To the acid solution was added (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8, 1.97 g, 5.0 mmol), 3-hydroxy1,2,3-benzotriazin-4(3*H*)-one (0.978 g, 6.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.15 g, 6.0 mmol) and triethylamine (2.8 mL, 20 mmol). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (50% ethyl acetate-hexane, then ethyl acetate) to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester (0.937 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 9.19 (s, 2H), 9.01 (s, 1H), 7.64 (d, 1H), 7.52 (d, 1H), 7.42 (dd, 1H), 7.33 (m, 5H), 6.20 (br d, 1H), 4.66 (m, 1H),

3.69 (s, 3H), 2.14 (t, 2H), 2.02 (s, 3H), 1.95 (m, 1H), 1.78 (m, 1H). MS (CI+) m/e 465 $(M+H)^+$.

Example 219C

[4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine

To a solution of the [4-(5-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester prepared in Example 210B (324 mg, 0.70 mmol) in methanol (2 mL) was added aqueous sodium hydroxide (2.0 N, 1.0 mL). After 14 hours, the reaction mixture was diluted with ethyl acetate (100 mL), washed twice with potassium dihydrogenphosphate (1.0 M, 20 mL each), water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was then purified by column chromatography (ethyl acetate, then 95:5:0.5 ethyl acetate-methanol-acetic acid)to give [4-(3-pyrimidylcarboxyamino)-2-phenylbenzoyl]methionine (265 mg, 84%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.80 (s, 1H), 9.38 (s, 1H), 9.30 (s, 2H), 8.51 (d, 1H), 7.83 (m, 2H), 7.50 (d, 1H), 7.39 (m, 5H), 4.29 (m, 1H), 2.28 (m, 2H), 2.00 (s, 3H), 1.86 (m, 2H). MS (APCI+) m/e 451 $(M+H)^+$.



Example 231

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

Example 231A

1-*tert*-butoxycarbonylpiperidine-3-carboxylic acid

To a mixture of piperidine-3-carboxylic acid (1.29 g, 10 mmol) in THF (20 mL) was added aqueous 4N sodium hydroxide (5 mL) and di-tert-butyldicarbonate (2.62 g, 12 mmol) and the reaction mixture was stirred for 6 hours. The reaction mixture was acidified with 3N HCl (7 mL) and extracted three times with ethyl acetate. The combined organic extracts were washed with water (2x) and brine, dried, filtered, and concentrated in vacuo to give 1-*tert*-butoxycarbonylpiperidine-3-carboxylic acid (2.11 g) as a white solid.

Example 231B

[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared by coupling of the product of Example 231A and (4-amino-2-phenylbenzoyl)methionine methyl ester (compound 8) according to the method of Example 186C.

Example 231C

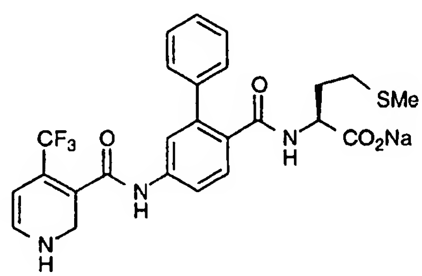
[4-(1-*tert*-butoxycarbonylpiperidin-3-ylcarboxyamino)-2-phenylbenzoyl]methionine

The desired compound was prepared by saponification of the product of Example 231B according to the procedure of Example 159.

Example 231D

[4-(3-piperidinecarboxyamino)-2-phenylbenzoyl]methionine hydrochloride

The product of Example 231C was deprotected with 4N HCl-dioxane using the procedure of Example 229B. ^1H nmr (300 MHz, D_2O) δ 7.37 - 7.60 (m, 8H), 4.44 (dd, 1H), 3.46 (dd, 1H), 3.31 (m, 2H), 1.14 (m, 1H), 3.02 (m, 1H), 1.71 - 2.11 (m, 8H), 2.02 (s, 3H). MS (CI NH_3) M/e 456 ($M+H^+$, 438, 408, 339, 307, 196. Anal calcd for $C_{24}H_{30}ClN_3O_4S{\bullet}2.54\ H_2O$: C, 53.60; H, 6.57; N, 7.59. Found: C, 53.60; H, 6.19; N 7.59.



Example 283

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

Example 283A

(4-nitro-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of (4-nitro-2-phenylbenzoyl)methionine methyl ester (7.69 g, 30 mmol), prepared as in Example 192A and aqueous saturated lithium hydroxide (20 mL) in methanol (50 mL) was refluxed for 6 hours. The reaction mixture was carefully acidified with

concentrated hydrochloric acid (10 mL), and extracted with ethyl acetate (4x). The combine extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in dichloromethane (50 mL) and THF (10 mL) and 2-trimethylsilylethanol (3.72 g, 31.5 mmol), 1,3-diisopropylcarbodiimide (5.17 mL, 33 mmol) and 4-dimethylaminopyridine (30 mg) were added sequentially. After 4 hours, aqueous hydrochloric acid (0.1 N, 0.5 mL) was added and the reaction mixture was stirred for another 2 hours. The reaction mixture was then filtered through silica gel (40 g), and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5% ethyl ether-hexane) to give the title compound (8.90 g, 87%).

Example 283B

(4-amino-2-phenylbenzoyl)methionine 2-trimethylsilylethyl ester

A mixture of the product of Example 283A (8.85 g, 25.8 mmol), ammonium formate (4.88 g, 77.4 mmol) and palladium (10%) on carbon (1 g) in methanol was refluxed for 5 hours. The mixture was then filtered through Celite and rinsed with ethyl acetate. The filtrate was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound which was used without further purification.

Example 283C

4-(4-trifluoromethylpyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A mixture of 4-trifluoromethylnicotinic acid (472 mg, 2.46 mmol), the product of Example 283B (771 mg, 2.46 mmol), 3-hydroxy1,2,3-benzotriazin-4(3*H*)-one (481 mg, 2.95 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (566 mg, 2.95 mmol) in DMF (8 mL) was stirred room temperature for 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (1.04 g, 87%).

Example 283D

4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoic acid 2-trimethylsilylethyl ester

A solution of the product of Example 283C (1.02 g, 2.09 mmol), tetrabutylammonium borohydride (539 mg, 2.1 mmol) in 1,2-dichloroethane (10 mL) was heated at 80 °C for 6 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate, water and brine, dried over anhydrous magnesium

sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (30% ethyl acetate-hexane) to give the title compound (247 mg, 24%).

Example 283E

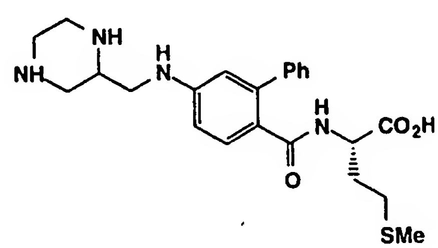
[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine methyl ester

A solution of the product of Example 283D (227 mg, 0.48 mmol) and tetrabutylammonium fluoride (261 mg, 1.0 mmol) in dioxane was heated at 80 °C for 90 min. The solvent was then evaporated, and the residue was further dried under high vacuum (2 mmHg) for 1 hour. To the residue was added *L*-methionine methyl ester hydrochloride (115 mg, 0.58 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (163 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (192 mg, 1.0 mmol), DMF (5 mL) and triethylamine (0.3 mL). After 15 hours, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (50% ethyl acetate-hexanes) to give the title compound (179 mg, 69%).

Example 283F

[4-(1H-4-trifluoromethyl-1,2-dihydropyrid-3-ylcarbonylamino)-2-phenylbenzoyl]methionine sodium salt

The desired compound was prepared by saponification of the product of Example 283E using the procedure of Example 276. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.87 (br s, 1H), 7.68 (m, 2H), 7.54 (s, 1H), 7.41-7.30 (m, 6H), 7.03 (dd, 1H), 6.51 (d, 1H), 4.67 (t, 1H), 4.48 (m, 1H), 3.78 (m, 1H), 2.14 (m, 2H), 1.96 (s, 3H), 1.77 (m, 2H). MS (APCI$^+$) m/e 520 (M+H)$^+$.



Example 286

[4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine

Example 286A

di-tert-butyoxycarbonylpiperidine-2-carboxylic acid

Di-*tert*-butyl dicarbonate (15.5 g, 70.2 mmol) was added to a solution of piperazine-2-carboxylic acid (4.85 g, 23.4 mmol) and NaOH (98 mL of a 1 M aqueous solution, 98 mmol) in THF (100 mL). The cloudy mixture was stirred for 16 hours and then was concentrated under reduced pressure to remove THF. The aqueous solution was saturated with $NaHCO_3$ (s) and then extracted with ether (2x). The aqueous layer was cooled to 0 °C and then adjusted to pH 3 with 2 M aqueous HCl during which time a precipitate formed. The mixture was extracted with CH_2Cl_2 (3x), and the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide the desired compound (7.61 g, 98% as a tan solid.

Example 286B

di-tert-butyoxycarbonylpiperidine-2-carboxylic acid *N*-methyl *N*-methoxy amide

Triethylamine (1.75 g, 17.1 mmol) was added dropwise to a solution of *N,O*-dimethylhydroxylamine hydrochloride (0.741 g, 7.44 mmol), the product of Example 286A (2.46 g, 7.44 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (1.61 g, 9.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.89 g, 9.67 mmol) in DMF (75 mL). The reaction mixture was stirred at ambient temperature for 20 hours and then concentrated under reduced pressure (50 °C, 0.1 mm Hg). The residue was dissolved in ethyl acetate (70 mL), and the solution was extracted with saturated aqueous $NaHCO_3$ (3x) and brine. The organic phase was dried ($MgSO_4$) and concentrated to provide a golden wax. Flash column chromatography (20% ethyl acetate-hexane) afforded the desired compound (2.29 g) which was shown to be 78% pure by ^{1}H NMR.

Example 286C

di-tert-butyoxycarbonylpiperidine-2-carboxaldehyde

A solution of the product of Example 286B (0.971 g, 2.81 mmol) in THF (4 mL) was added dropwise to a slurry of LAH (0.112 g, 2.81 mmol) in THF (4 mL) at -50 °C. After 10 minutes the bath temperature was adjusted to -10 °C for 10 min and then returned to -50 °C. The addition of saturated aqueous $KHSO_4$ (8 mL) produced vigorous gas evolution, after which reaction mixture was allowed to warm to ambient temperature over 20 minutes and then filtered through Celite. The filtrate was extracted with 1 N HCl (2x), saturated aqueous $NaHCO_3$ (2x) and finally brine. The organic phase was dried ($MgSO_4$) and concentrated to provide the desired compound (0.304 g, 41%) as an amber oil.

Example 286D

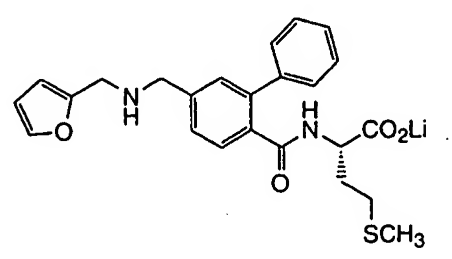
[4-(*di-tert*-butoxycarbonylpiperazin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

The aldehyde prepared in Example 286C (0.599 g, 1.71 mmol) was added to a solution of *N*-(4-amino-2-phenylbenzoyl)methionine methyl ester hydrochloride (1.01 g, 2.05 mmol), prepared as in Example 192B, sodium acetate (0.425 g, 5.13 mmol) and acetic acid (0.205 g, 3.42 mmol) in isopropanol (7 mL). After 1 hour, $Na(CN)BH_3$ (0.147 g, 2.22 mmol) was added in two portions and the mixture was stirred for 15 hours before concentration under reduced pressure provided a waxy residue. Flash column chromatography (hexane-ethyl acetate-triethylamine 60:38:2) followed by radial chromatography eluting with 40% ethyl acetate-hexane) afforded the title compound (0.344 g, 31%) as a white foam. ^1H NMR ($CDCl_3$): d 1.35-1.52 (comp, 18H), 1.52-1.71 (m, 1 H), 1.71-1.93 (m, 1 H), 2.02 (s, 3 H), 2.02-2.20 (comp, 2 H), 2.80-3.12 (comp, 2 H), 3.12-3.33 (br, 1 H), 3.33-3.50 (br, 1 H), 3.64 (s, 3 H), 3.83-4.28 (br, 3 H), 4.28-4.45 (br, 1 H), 4.60-4.72 (br, 1 H), 5.63-5.74 (br, 1 H), 6.44-6.58 (br, 1 H), 6.58-6.80 (br, 1 H), 7.33-7.52 (comp, 5 H), 7.72 (d, 1 H). LRMS (CI): 657 $(M+1)^+$.

Example 286E

[4-(2-piperazinylmethylamino)-2-phenylbenzoyl]methionine

Sodium hydroxide (0.642 mL of a 0.979 M aqueous solution, 0.629 mmol) was added to a solution of the product of Example 286D (0.344 g, 0.524 mmol) in methanol (2 mL). After 5 hours the mixture was lyopholized, and the resulting white foam was treated with HCl (4.7 mL of a 4 M dioxane solution, 18.8 mmol). After 7 hours, pentane was added and the yellow precipitate was isolated by filtration to afford the desired compound (79.3 mg, 24%) as the bis-hydrochloride, mono-sodium chloride salt. ^1H NMR (300 MHz, CD_3OD) d 1.71-1.85 (m, 1H), 1.91-2.00 (m, 1H), 2.02 (s, 3H), 2.02-2.15 (m, 1H), 2.15-2.27 (m, 1H), 3.32-3.56 (comp, 3H), 3.56-3.75 (comp, 4H), 3.75-3.96 (br, 2H), 4.45 (dd, 1H), 6.73 (s, 1H), 6.81 (d, 1H), 7.30-7.50 (comp, 6H). LRMS (CI) m/e 443 $(M+H)^+$.



Example 302

[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine lithium salt

Example 302A

4-(2-furylmethylaminomethyl)-2-phenylbenzoic acid methyl ester

To a stirred soltuion of 4-carboxaldehyde-2-phenylbenzoic acid methyl ester (0.73 g, 3.0 mmol), prepared as in Example 160B, in methanol (15 mL) was added furfurylamine (0.33 g, 3.4 mmol), sieves (~ 1g), $NaBH_3CN$ (0.29 g, 4.6 mmol) and acetic acid (~0.3 mL) to pH = 6. The mixture was stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo and the residue was taken up in ethyl acetate and filtered through a short bed of silica gel. The bed was washed with ethyl acetate and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (CH_2Cl_2-ethyl acetate 9:1) to give the desired compound (0.72 g, 73%) as an opaque yellow paste.

Example 302B

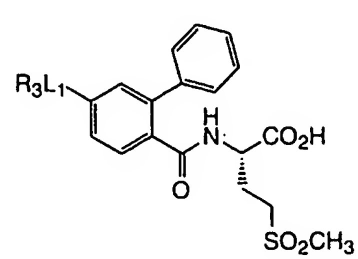
[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

The desired compound was prepared by saponification of the product of Example 302A, followed by coupling with methionine methyl ester hydrochloride according to the method of Examples 299C and D.

Example 302C

[4-(2-furylmethylaminomethyl)-2-phenylbenzoyl]methionine methyl ester

To a stirred solution of the product of Example 302B (56 mg, 0.12 mmol) in THF (2 mL) was added a solution of $LiOH{\cdot}H_2O$ (5.5 mg, 0.13 mmol) in H_2O (1 mL) and the resulting solution stirred for 3 hours at ambient temperature. The reaction was concentrated in vacuo, diluted with H_2O, filtered and lyophilized to give the title compound (57 mg, 97%) as a white powder. ^1H NMR (300 MHz, DMSO-d6, 90 ^oC) δ 7.48-7.24 (m, 9H), 7.07-7.04 (m, 1H), 6.37-6.34 (m, 1H), 6.24-6.20 (m, 1H), 3.76-3.69 (m, 5H), 2.43-2.16 (m, 3H), 2.00-1.66 (m, 5H). MS *m/z* 439 (M+ 1)$^+$. Anal calcd for $C_{24}H_{25}LiN_2O_4S{\cdot}2\ H_2O$ (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.

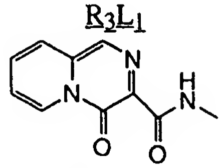
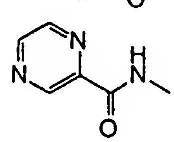


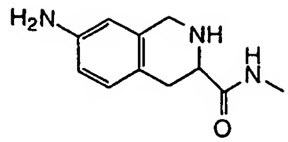
Examples 350-357

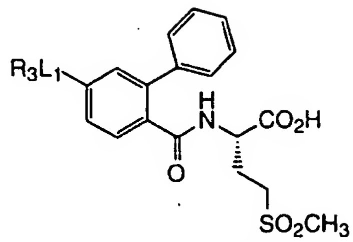
All reactions were performed either in a Manual solid phase synthesis flask using a 120o rotary shaker or on an Advanced ChemTech Model 396 Multiple Peptide Synthesizer (Advanced ChemTech Inc.; Louisville, Kentucky) at ambient temperature.

After the reactions were performed the finished compounds were cleaved from the resin. Usually, 80-90 mg of the dried resin containing the desired amide; urea; or secondary amine was treated with a 1.50 mL solution of 95/5 (v:v) trifluoroacetic acid/water for 1.5 h at ambient temperature. The spent resin was removed by filtration and the resulting cleavage solution evaporated in-vacuo. In most cases, 5- 20 mg of crude compound was obtained. Compounds obtained had the desired MW as determined by electrospray mass spectroscopy and had an HPLC purity of 40-90%, or were further purified by partition chromatography to afford compounds of 40-60% HPLC purity. Two types of gradients were used for the reverse phase HPLC. For the amides and ureas a gradient starting with 100% water-0.1% Trifluoroacetic acid and finishing with 100% acetonitrile-0.1% Trifluoracetic acid during a 30 minute period was used. For the secondary amines a gradient beginning with 100% water-5mmol ammonium acetate and finishing with 80% acetonitrile-water-5mmol ammonium acetate during 25 minutes was used.

80 mg of resin (substitution 0.40 mmol/g) containing [4-amino-2-phenylbenoyl]methionine-Wang-polystyrene resin was shaken for 3 min. with 1.0 mL. of N-methylpyrrolidone (NMP). The solvent was drained and the resin was treated 2x (3 min) with 1 mL. NMP. To the now swollen resin were then added 0.20 mL NMP; 0.20 mL of a 1.92 M diisopropylethylamine (DIEA)/NMP solution (15 eq.); 1.00 mL of a 0.180 mM/NMP solution of the desired carboxylic acid (5 eq.); and finally 0.20 mL of a 0.90 M Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop; 5 equiv.)1/NMP solution. The reaction slurry was then mixed for 6 h and drained. The resin was then washed with NMP (3x; 1.0 mL; 3 min. ea); isopropanol (IPA; 5x; 1.0 mL; 3 min. ea.); NMP (3x; 1.0 mL; 3 min. ea.); methanol (MEOH; 2x; 1.0 ml; 3 min. ea.); and finally diethyl ether (2x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage conditions described above.

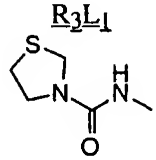
Example	R_3L_1	MS $(M+H)^{\pm}$
354		531
355		451

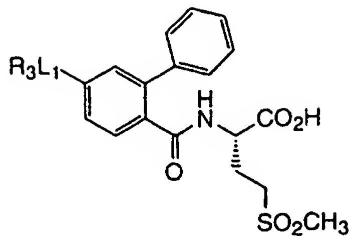
356		519



Examples 358

90 mg of resin (substitution 0.39 mmol/g.) containing [4-amino-2-phenylbenzoyl]methionine-Wang-polystyrene resin was shaken with 1.0 mL. dimethylformamide (DMF) for 3 min. The solvent was drained and the resin was then washed with DMF (3x; 1.0 mL; 3 min. ea.); tetrahydrofuran (THF; 4x; 1.0 mL; 3 min. ea.); THF/dichloromethane (DCM) 1:1 (v:v) (4x; 1.0 mL; 3 min. ea.). The resin was then treated with 0.20 mL of DCM/THF (1:1) and a 1.0 mL solution of 0.50 M p-Nitrophenylchloroformate/0.50 M DIEA in a 1:1 solvent mixture of DCM/THF. The resin suspension was then shaken for 15 min. and to the suspension was then added .020 mL of neat DIEA. After shaking for an additional 15 min.; the solvents were drained away and the resin was then washed with DCM/THF (1:1) (4x; 1.0 mL; 3 min. ea.) The resin was then treated with 0.20 mL of DMF and 1.0 mL of a DMF solution containing 0.50 M of the desired primary or secondary amine and 0.50 M of DIEA. The suspension was shaken for 30 min. The solvent was drained off and the resin was then washed with DMF (4x; 1.0 mL; 3 min. ea); THF (4x; 1.0 mL; 3 min. ea.); DCM/THF (4x; 1.0 mL; 3 min. ea); diethyl ether (4x; 1.0 mL; 3 min. ea.). The resin was then dried and subjected to cleavage from the resin as described above.

Example	R_3L_1	MS $(M+H)^+$
358		460



Examples 360-362

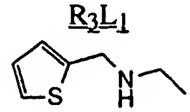
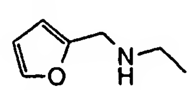
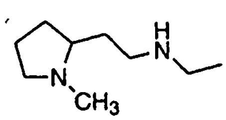
Examples 364-366

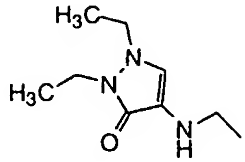
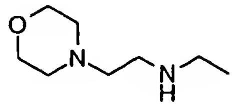
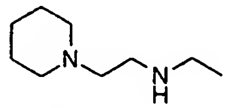
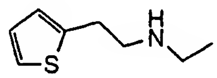
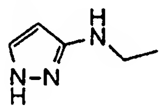
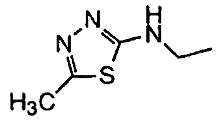
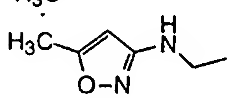
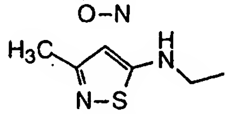
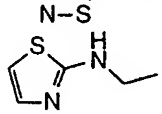
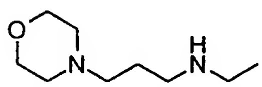
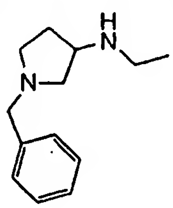
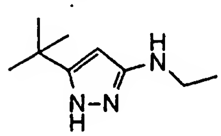
Examples 369-374

Examples 377-378

Example 381

Typically 80 mg of resin (substitution of 0.40 mmol/g) containing 4-formyl-2-phenylbenzamide-L-Methionine-Wang-polystyrene resin was swollen with 1.0 mL of dimethyl acetamide (DMA) for 3 min. The solvent was drained and the resin was then washed with additional DMA (2x; 1.0 mL; 3 min. ea.). The resin was then suspended in 0.20 mL of DMA and to the suspension was then added a 1.0 mL solution containing 0.48 mM of the desired primary amine (10 eq.) in a 3:1 (v:v) solution of DMA/acetic acid. The resin was shaken for 2 h and was then treated with 0.25 mL of a 2.4 mM solution of sodium cyanoborohydride (10 eq.) in DMA. The resin-slurry was shaken for an additional 2 h. The solvents were drained and the resin was then washed with DMA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min. ea.); IPA (6x; 1.0 mL; 3 min. ea.); DMF (6x; 1.0 mL; 3 min. ea.); MEOH (6x; 1.0 mL; 3 min. ea.); diethyl ether (6x; 1.0 mL; 3 min. ea.). The resin was dried and then subjected to cleavage as described above.

Example	R_3L_1	MS $(M+H)^{\pm}$
360		455
361		439
362		471

364		498
365		473
366		471
369		470
370		425
371		458
372		441
373		457
374		443
377		487
378		573
381		481

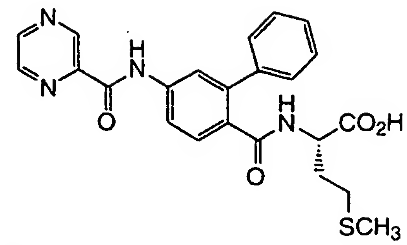
7540

Examples 395 and Example 398

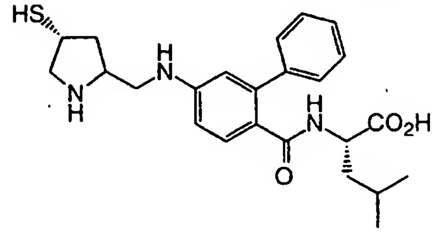
The following compounds were prepared using the materials and methods described above.

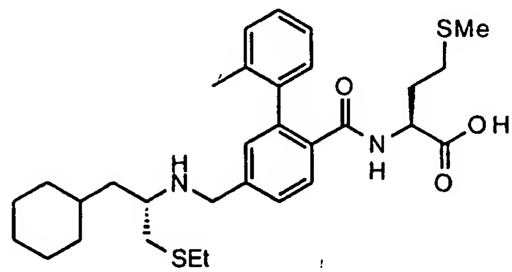
Example

395



398

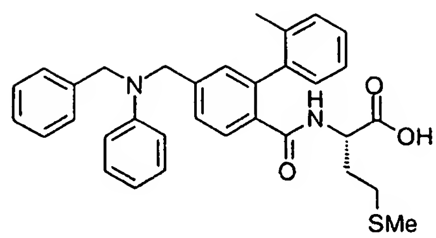




Example 403

[4-(1-ethylthio-3-cyclohexylprop-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl] methionine.

The desired compound was prepared according to the method of Example 349A except substituting (S)-(+)-1-ethylthio-3-cyclohexyl-2-propylamine hydrochloride for (S)-(+)-2-amino-3-cyclohexyl-1-propanol hydrochloride. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.02 (m, 1H), 7.50-7.38 (m, 2H), 7.22-7.05 (m, 4H), 4.21 (m, 1H), 3.88-3.78 (m, 2H), 2.74-2.60 (m, 2H), 2.51 (s, 3H), 2.44 (q, J=7.5 Hz, 2H), 2.22-1.95 (m, 5H), 1.88-1.50 (m, 7H), 1.45-1.25 (m, 4H), 2.21-1.02 (m, 3H), 1.12 (t, J=7.5 Hz, 3H), 0.90-0.70 (m, 2H). MS (CI/NH_3) m/e: 557 $(M+H)^+$ Anal calcd for $C_{31}H_{44}N_2O_3S_2 \cdot 1.15\ H_2O$: C, 64.47; H, 8.08; N, 4.85. Found: C, 64.48; H, 7.84; N, 4.72.



Example 406

4-(N-benzyl-N-phenyl)-aminomethyl-2-(2-methylphenyl)benzoylmethionine

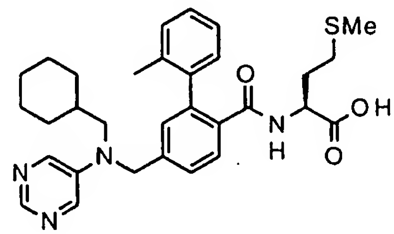
The desired compound was prepared according to Example 273 except substituting N-benzylaniline for 2-thiophenemethanol in Example 273A.

^{1}H NMR (CD$_3$OD): δ 1.62-1.77 (m, 1 H), 1.86-2.07 (comp, 7 H), 2.07-2.18 (comp, 2 H), 4.37-4.47 (br, 1 H), 4.70-4.84 (comp, 4 H), 6.68-6.89 (br, 3 H), 7.08-7.32 (comp, 13 H), 7.35-7.40 (m, 1 H), 7.56-7.62 (m, 1 H). LRMS (CI): 539 (M+1)$^+$.

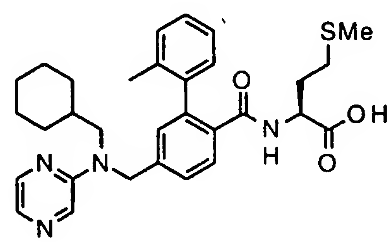
Examples 411-417

The following compounds are prepared according to the method of Example 407 except substituting the desired N-benzyl- or N-cyclolhexylmethylaminopiperazine for N-benzyl-3-aminopyridine.

411



412



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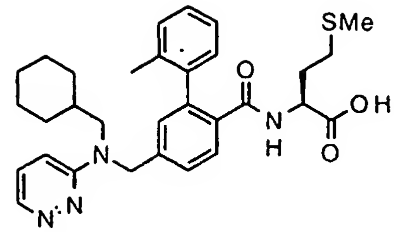

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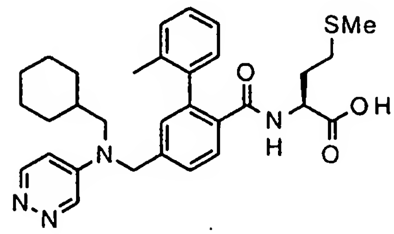

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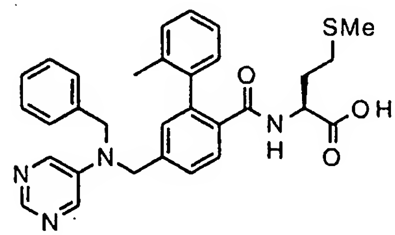

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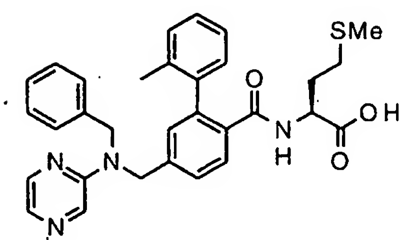
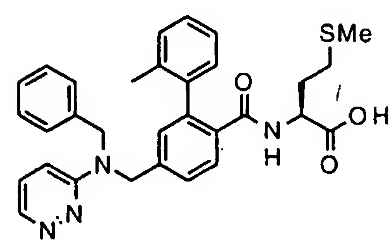


416A



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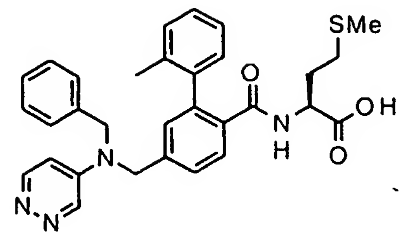
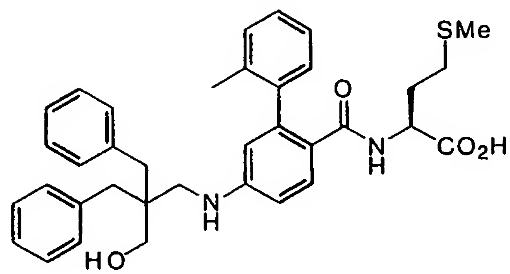
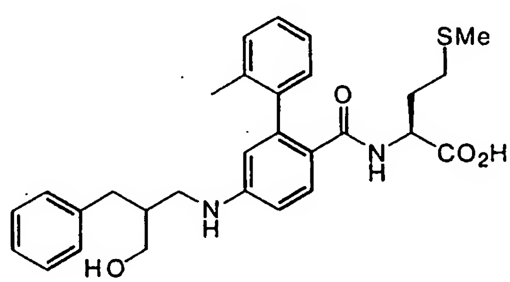




Example 475

N-[4-N-(2,2-dibenzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine sodium salt

The desired compound was prepared according to the method of Examples 25A -25B ^1H nmr (300 MHz, DMSO-d_6): δ 7.40 (d, 1 H), 7.25-7.10 (m, 15 H), 6.65 (m, 1 H), 6.27 (d, 1 H), 6.08 (m, 1 H), 4.84 (m, 1 H), 3.70 (m, 1 H), 3.17 (br s, 2 H), 3.03 (br s, 2 H), 2.80 (AB q, 4 H), 2.18 (m, 1 H), 1.99,1.91 (2 br s's, 6 H), 1.97 (m, 1 H), 1.70-1.50 (m, 2 H). MS (APCI +) m/e 597 $(M+H)^+$.

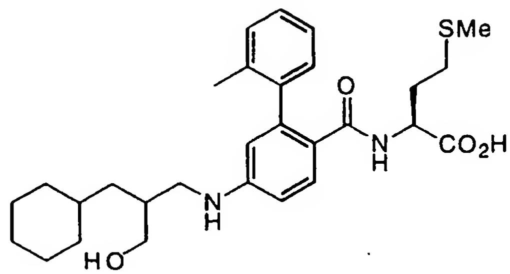


Example 476

N-[4-N-(2-benzyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine sodium salt

The desired compound was prepared according to the method of Examples 25A -25B ^1H nmr (300 MHz, DMSO-d_6): δ 7.35 (d, 1 H), 7.28-7.10 (m, 10 H), 6.50 (m, 1 H), 6.16 (d, 1 H), 6.05 (m, 1 H), 4.55 (m, 1 H), 3.64 (m, 1 H), 3.39 (m, 2 H), 2.62 (m, 2 H), 2.38

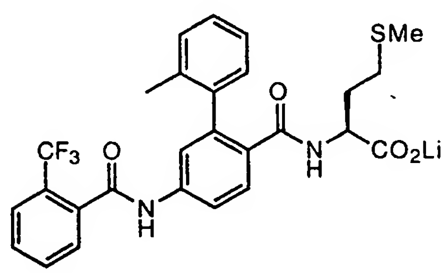
(m, 1 H), 2.15 (m, 1 H), 1.97,1.91 (2 br s's, 6 H), 1.95 (m, 2 H), 1.70-1.50 (m, 2 H) (note: the methylene protons adjacent to the NH group might be buried in the residue water pk of DMSO). MS (APCI +) m/e 506 $(M+H)^+$.



Example 479

N-[4-N-(2-cyclohexylmethyl-3-hydroxypropyl)amino-2-(2-methylphenyl)benzoyl]methionine

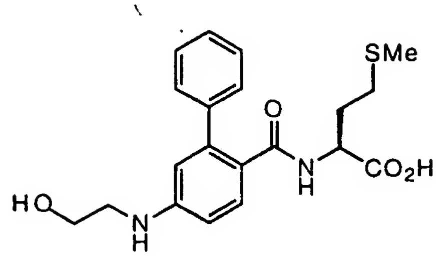
The desired compound was prepared according to the method of Examples 25A -25B ^1H nmr (300 MHz, DMSO-d_6): δ 7.37 (d, 1 H), 7.16 (m, 3 H), 7.02 (d, 1 H), 6.93 (m, 1 H), 6.58 (m, 1 H), 6.00 (m, 1 H), 4.45 (m, 1 H), 3.65 (m, 1 H), 3.38 (m, 2 H), 2.19 (m, 1 H), 2.03,1.97,1.93,1.92 (4 s's, 6 H), 1.96 (M, 1 H), 1.90-0.75 (m's, 14 H). MS (ESI –): m/e 511 $(M-H)^-$.



Example 481

N-[4-N-(4-trifluoromethylnicotinoyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

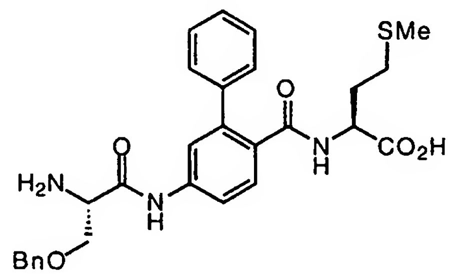
The desired compound was prepared according to the method of Example 57. ^1H nmr (300 MHz, DMSO-d_6): δ 11.04 (br s, 1 H), 9.05 (s, 1 H), 8.98 (d, 1 H), 7.90 (d, 1 H), 7.69 (br d, 1 H), 7.57 (m, 2 H), 7.23 (m, 4 H), 6.97 (m, 1 H), 3.70 (m, 1 H), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.91 (br s, 6 H), 1.70 (m, 1 H), 1.58 (m, 1 H). MS (ESI –): m/e 530 $(M-H)^-$.



Example 502

N-[4-N-2-hydroxyethylamino-2-phenylbenzoyl]methionine

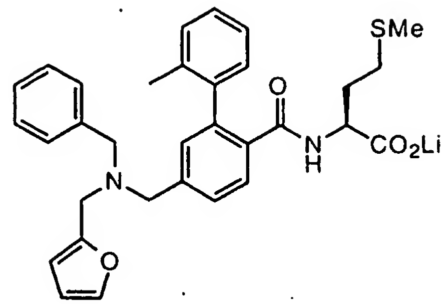
The desired compound was prepared according to the method of Example 57, employing t-butyl bromoacetate. The resultant t-butyl ester was treated with TFA, and then reduced with borane. ^{1}H NMR (CD_3OD): δ 1.68-1.81 (m, 1 H), 1.89-2.10 (m, 1 H), 2.01 (s, 3 H), 2.02-2.24 (comp, 2 H), 3.28 (t, J= 5.9 Hz, 2 H), 3.72 (t, J= 5.9 Hz, 2 H), 4.44 (dd, J= 4.4, 9.2 Hz, 1 H), 6.57 (d, J= 2.3 Hz, 1 H), 6.65 (dd, J= 2.4, 8.5 Hz, 1 H), 7.28-7.44 (comp, 6 H). LRMS (CI): 389 $(M+1)^+$



Example 503

N-[4-(N-2-amino-3-benzyloxypropionyl)amino-2-phenylbenzoyl]methionine

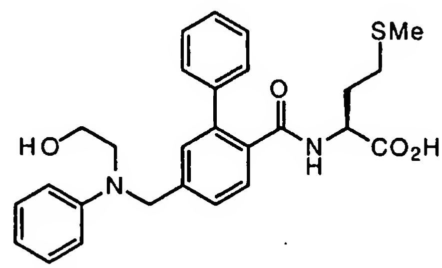
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (CD_3OD): δ 1.71-1.88 (m, 1 H), 1.90-2.28 (comp, 6 H), 3.65-3.72 (m, 1 H), 3.86-3.94 (comp, 2 H), 4.24-4.31 (m, 1 H), 4.44-4.56 (m, 1 H), 4.62 (dd, J= 12.2, 29.2 Hz, 2 H), 7.23-7.58 (comp, 11 H), 7.62-7.70 (comp, 2 H). LRMS (CI): 522 (M+1 of free base)$^+$



Example 504

N-[4-N-(furan-2-ylmethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

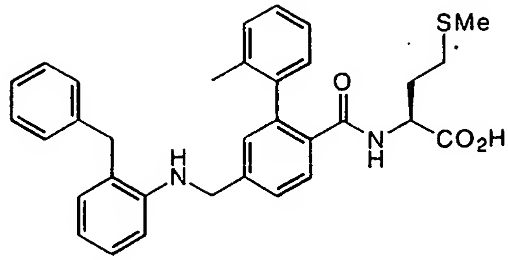
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (CD_3OD): δ 1.57-1.70 (m, 1 H), 1.75-1.92 (comp, 2 H), 1.94-2.01 (comp, 6 H), 2.01-2.09 (br, 1 H), 3.56-3.67 (comp, 6 H), 4.17-4.29 (br, 1 H), 6.20-6.23 (m, 1 H), 6.33-6.36 (m, 1 H), 7.07-7.33 (comp, 8 H), 7.33-7.40 (comp, 2 H), 7.42-7.49 (comp, 2 H), 7.60-7.67 (m, 1 H). LRMS (CI): 543 (M+1 of protonated acid)$^+$.



Example 505

N-[4-N-phenyl-N-benzylaminomethyl-2-phenylbenzoyl]methionine

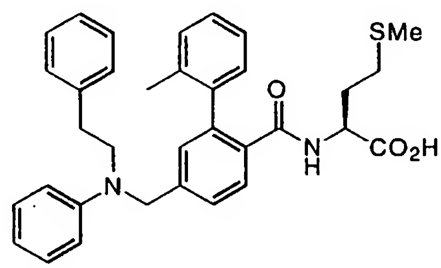
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d_6-DMSO): δ 1.73-1.96 (comp, 2 H), 1.99 (s, 3 H), 2.12-2.32 (comp, 2 H), 5.53-3.66 (comp, 2 H), 3.72-3.76 (br s, 1 H), 4.24-4.33 (comp, 2 H), 4.57-4.61 (br s, 1 H), 4.72 (s, 2 H), 6.58-6.96 (comp, 3 H), 7.06-7.19 (comp, 2 H), 7.25-7.42 (comp, 8 H), 8.53 (d, J= 7.7 Hz, 1 H). LRMS (CI): 479 (M+1)$^+$.



Example 506

N-[4-N-(2-benzylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

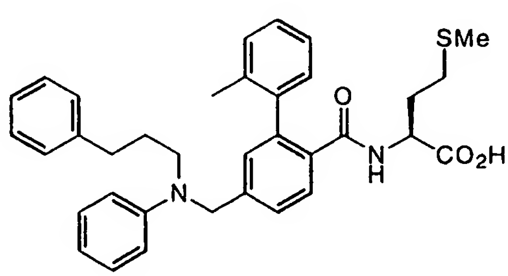
The desired compound was prepared according to the method of Example 157 ^1H NMR (CD_3OD): δ 1.63-1.80 (br, 1 H), 1.87-2.07 (br, 7 H), 2.07-2.23 (comp, 2 H), 4.02 (s, 2 H), 4.38-4.51 (comp, 3 H), 6.87-6.93 (br, 1 H), 6.96-7.44 (comp, 14 H), 7.58-7.64 (m, 1 H). LRMS (CI): 539 $(M+1)^+$, 556 $(M+NH_4)^+$.



Example 507

N-[4-N-(2-phenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

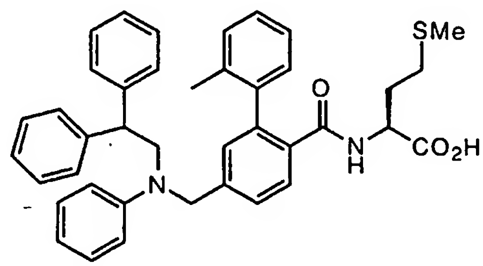
The desired compound was prepared according to the method of Example 157 ^1H NMR (CD_3OD): δ 1.55-1.68 (m, 1 H), 1.71-2.12 (comp, 9 H), 2.92 (t, 2 H), 3.63-3.71 (m, 2 H), 4.16-4.27 (br, 1 H), 4.52 (s, 2 H), 6.64 (t, 1 H), 6.74 (d, 2 H), 6.99-7.30 (comp, 13 H), 7.60 (d, 1 H). LRMS (ESI^-): 551 $(M-1)^-$.



Example 508

N-[4-N-(3-phenyl)propyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

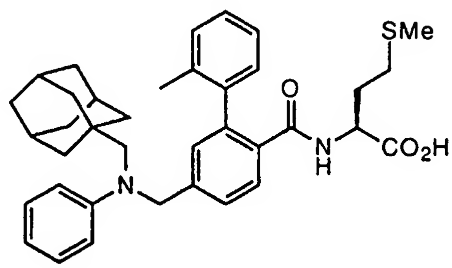
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (CD_3OD): δ 1.45-1.62 (m, 1 H), 1.63-2.05 (comp, 11 H), 2.52-2.61 (m, 1 H), 3.30-3.39 (m, 2 H), 4.08-4.19 (br, 1 H), 4.50 (s, 2 H), 6.49-6.56 (comp, 3 H), 6.92-7.23 (comp, 13), 7.49-7.56 (m, 1 H). LRMS (ESI$^-$): 565 $(M-1)^-$.



Example 509

N-[4-N-(2,2-diphenyl)ethyl-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

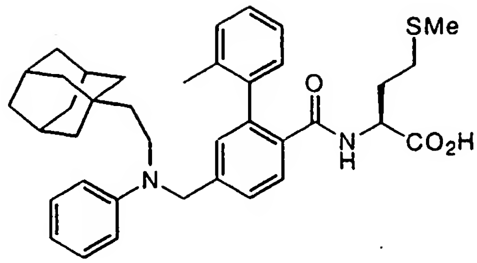
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d_6-DMSO): δ 1.46-2.02 (comp, 10 H), 3.38-3.42 (m, 1 H), 3.61-3.73 (br ,1 H), 4.16 (d, J= 7.3 Hz, 2 H), 4.31 (s, 2 H), 4.40-4.47 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.78 (s, 1 H), 6.82-6.94 (br, 1 H), 7.05-7.21 (comp, 8 H), 7.22-7.30 (comp, 4 H), 7.35-7.41 (comp, 5 H). LRMS (CI): 629 $(M+1)^+$.



Example 510

N-[4-N-(adamantan-1-ylmethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

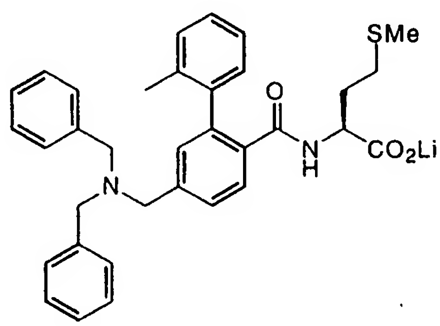
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d_6-DMSO): δ 1.48-2.20 (br, comp, 25 H), 3.16-3.31 (br m, 1 H), 3.40-4.30 (br comp, 4 H), 4.65-4.74 (br m, 1 H), 6.49-6.57 (br m, 1 H), 6.68-6.75 (br comp, 2 H), 6.85-7.12 (br comp, 3 H), 7.14-7.25 (br comp, 5 H), 7.45 (d, J= 8.0 Hz, 1 H). LRMS (CI): 597 $(M+1)^+$.



Example 511

N-[4-N-(2-adamantan-1-ylethyl)-N-phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

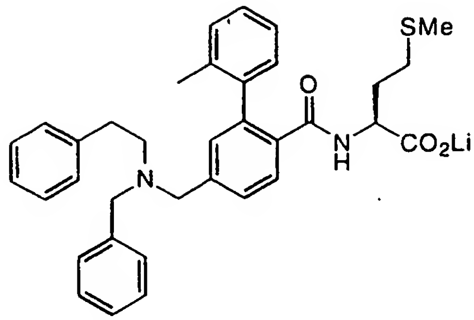
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d$_6$-DMSO): δ 1.28-1.37 (comp, 2 H), 1.47-1.71 (comp, 15 H), 1.88-2.10 (comp, 11 H), 3.33-3.47 (br comp, 2 H), 3.61-3.69 (br m, 1 H), 4.54 (s, 2 H), 6.55 (t, *J*= 7.1 Hz, 1 H), 6.63 (d, *J*= 8.1 Hz, 2 H), 6.88-6.94 (br m, 1 H), 6.97 (d, *J*= 1.3 Hz, 1 H), 7.07-7.21 (comp, 5 H), 7.27 (dd, *J*= 1.7, 7.8 Hz, 1 H), 7.49 (d, *J*= 8.2 Hz, 1 H). LRMS (ESI$^-$): 609 (M-1)$^-$.



Example 512

N-[4-N,N-dibenzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

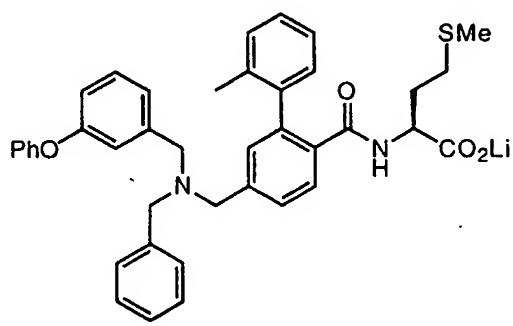
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (d$_6$-DMSO): δ 1.44-2.17 (comp, 10 H), 3.33-3.77 (comp, 7H), 6.90-7.56 (comp, 17 H). LRMS (ESI$^-$): 551 (M-1 of protonated acid)$^-$.



Example 513

N-[4-N-(2-phenylethyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

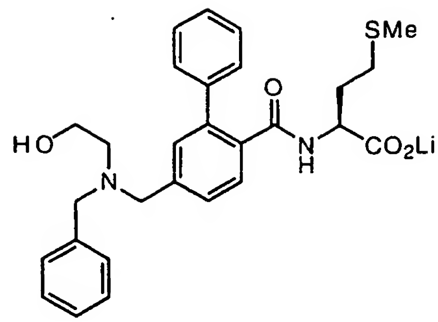
The desired compound was prepared according to the method of Example 158 ^1H NMR (d_6-DMSO): δ 1.65-1.90 (comp, 2 H), 1.96 (s, 3 H), 1.98-2.24 (comp, 5 H), 3.04-3.20 (comp, 4 H), 4.17-4.32 (br, 1 H), 4.36-4.56 (br, 4 H), 7.03-7.34 (comp, 12 H), 7.43-7.53 (br, 3 H), 7.54-7.63 (comp, 2 H), 7.67-7.76 (comp, 2 H), 7.76-7.84 (m, 1 H), 8.32 (d, *J*= 7.3 Hz, 1 H), 11.42-11.64 (br, 1 H), 12.35-12.55 (br, 1 H). LRMS (CI): 567 $(M+1)^+$.



Example 514

N-[4-N-(3-phenoxybenzyl)-N-benzylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

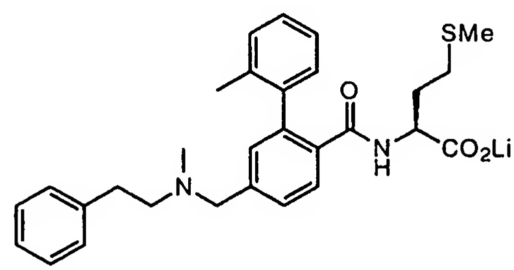
The desired compound was prepared according to the method of Example 158 ^1H NMR (d_6-DMSO): δ 1.65-1.90 (comp, 2 H), 1.95 (s, 3 H), 1.96-2.22 (comp, 5 H), 3.42-3.58 (br, 2 H), 4.15-4.39 (comp, 5 H), 6.88-7.62 (comp, 19 H), 7.64-7.71 (m, 1 H), 8.05-8.22 (m, 1 H), 11.30-11.44 (br, 1 H). LRMS (CI): 645 $(M+1)^+$.



Example 515

N-[4-N-(2-hydroxyethyl)-N-benzylaminomethyl-2-phenylbenzoyl]methionine lithium salt

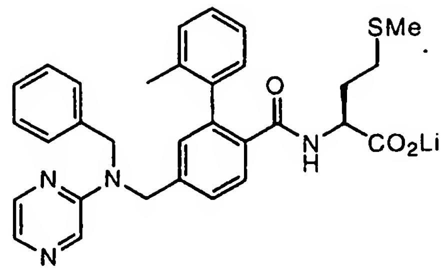
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (d_6-DMSO): δ 1.75-1.97 (comp, 2 H), 2.00 (s, 3 H), 2.15-2.34 (comp, 2 H), 3.00-3.11 (br m, 2 H), 3.79-3.87 (br m, 2 H), 4.28-4.51 (comp, 5 H), 7.32-7.43 (comp, 3 H), 7.43-7.55 (comp, 6 H), 7.64-7.79 (comp, 4 H), 8.66 (d, J= 7.7 Hz, 1 H). LRMS (CI): 493 $(M+1)^+$.



Example 516

N-[4-N-methyl-N-(2-phenyethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

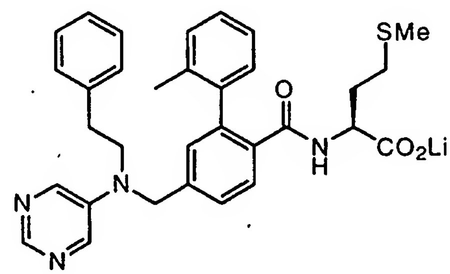
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (d_6-DMSO): δ 1.65-1.91 (comp, 2 H), 1.96 (s, 3 H), 1.99-2.28 (comp, 5 H), 2.75 (s, 1 H), 3.05-3.25 (comp, 2 H), 3.25-3.44 (comp, 2 H), 4.17-4.30 (br, 1 H), 4.30-4.40 (m, 1 H), 4.46-4.56 (m, 1 H), 7.07-7.38 (comp, 9 H), 7.47-7.60 (comp, 2 H), 7.68-7.75 (m, 1 H), 8.33 (d, J= 7.0 Hz, 1 H), 11.10-11.26 (br, 1 H), 12.50-12.86 (br, 1 H). LRMS (CI): 491 $(M+1)^+$.



Example 517

N-[4-N-benzyl-N-pyrazin-2-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

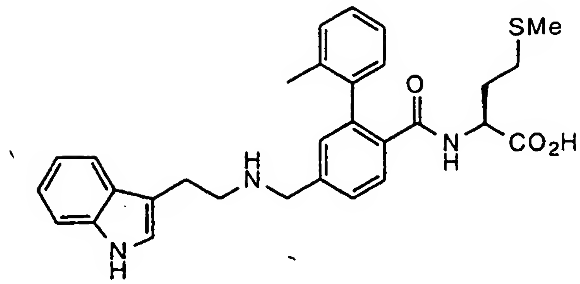
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d_6-DMSO): δ 1.46-2.09 (comp, 10 H), 3.59-3.70 (br, 1 H), 4.83-4.95 (comp, 4 H), 6.90-6.95 (br, 1 H), 7.00 (s, 1 H), 7.04-7.34 (comp, 10 H), 7.49 (d, *J*= 8.1 Hz, 1 H), 7.80 (d, *J*= 2.6 Hz, 1 H), 8.04-8.05 (m, 1 H), 8.07-8.10 (m, 1 H). LRMS (ESI$^-$): 539 (M-1 of protonated acid)$^-$.



Example 518

N-[4-N-(2-phenyethyl)-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

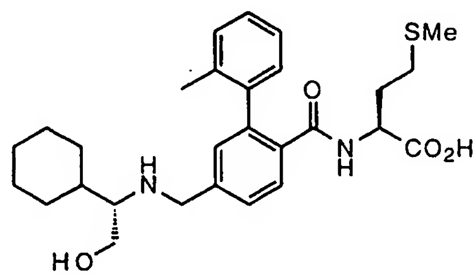
The desired compound was prepared according to the method of Example 157 ^{1}H NMR (d_6-DMSO): δ 1.46-2.05 (comp, 10 H), 2.88 (t, *J*= 7.5 Hz, 2 H), 3.56-3.65 (br, 1 H), 3.73 (t, *J*= 7.5 Hz, 2 H), 4.66 (s, 2 H), 6.90-7.01 (br comp, 2 H), 7.05-7.31 (comp, 10 H), 7.49 (d, *J*= 7.8 Hz, 1 H), 8.23 (s, 2 H), 8.41 (s, 1 H). LRMS (ESI$^-$): 553 (M-1 of protonated acid)$^-$.



Example 519

N-[4-N-(2-indol-3-ylethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

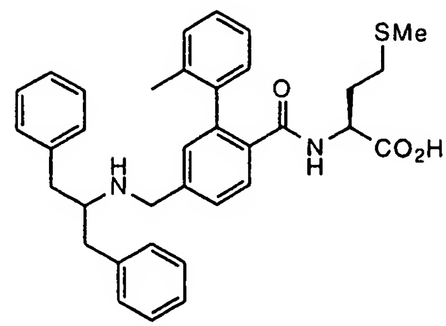
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (300 MHz, DMSO) δ 1.48-1.75 (m, 2H), 1.75-1.97 (m, 3H), 1.93 (s, 3H), 1.99 (m, 2H), 2.06-2.15 (m, 2H), 2.74-2.87 (m, 4H), 3.65 (brs, 1H), 3.79 (m, 2H), 6.88-6.93 (m, 1H), 6.93 (ddd, J=6.8, 6.8, 1.0 Hz, 1H), 7.03 (ddd, J=6.8, 6.8, 1 Hz, 1H), 7.10 (d, J=2.1 Hz, 1H), 7.10-7.23 (m, 5H), 7.30 (d, J=8 Hz, 1H), 7.36 (dd, J=8 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H). MS (ESI(+)) m/z 516 $(M+H)^+$. Anal calcd for $C_{30}H_{32}N_3O_3SLi{\bullet}1.30H_2O$: C, 66.11; H, 6.40; N, 7.71. Found: C, 66.15; H, 6.38; N, 7.64.



Example 520

N-[4-N-(2-cyclohexyl-1-ethan-1-ol-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

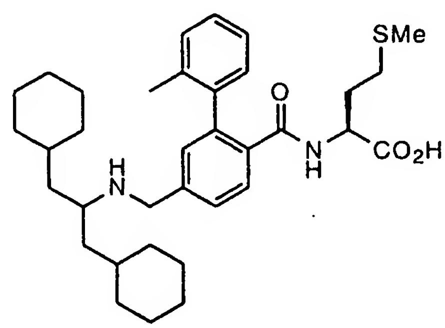
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (300 MHz, DMSO) δ 0.93-1.19 (m, 6H), 1.35-1.77 (m, 4H), 1.77-2.06 (m, 7H), 1.91 (s, 3H), 2.18 (brs, 1H), 2.26 (m, 3H), 3.40-3.48 (m, 1H), 3.59-3.70 (m, 1H), 3.73 (d, J=14.2 Hz, 1H), 3.81 (d, J=13.9 Hz, 1H), 4.36 (brs, 1H), 6.87-7.00 (m, 1H), 7.11-7.27 (m, 5H), 7.36 (d, J=8 Hz, 1H), 7.47 (d, J=8 Hz, 1H). MS (ESI(+)) m/z 499 $(M+H)^+$. Anal calcd for $C_{28}H_{37}N_2O_4SLi{\bullet}0.75H_2O$: C, 64.91; H, 7.49; N, 5.41. Found: C, 64.92; H, 7.39; N, 5.21.



Example 523

N-[4-N-(1,3-diphenylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 1.48-1.74 (m, 2H), 1.74-2.02 (m, 3H), 1.93 (s, 3H), 2.03-2.14 (m, 2H), 2.54-2.73 (m, 4H), 2.97 (pentet, J=6.5 Hz, 1H), 3.63-3.72 (brs, 1H), 3.78 (s, 2H), 6.90 (brs, 2H), 7.05-7.26 (m, 16H), 7.37 (d, J=7.8 Hz, 1H). MS (ESI(+)) m/z 567 $(M+H)^+$. Anal calcd for $C_{35}H_{37}N_2O_3SLi \cdot 0.90H_2O$: C, 71.38; H, 6.64; N, 4.76. Found: C, 71.40; H, 6.28; N, 4.69.

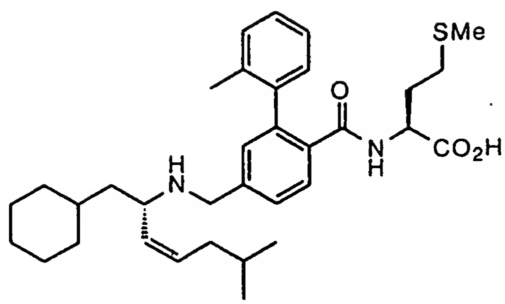


Example 524

N-[4-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 0.70-0.88 (m, 4H), 1.01-1.17 (m, 8H), 1.20-1.38 (m, 4H), 1.46-1.64 (m, 12H), 1.64-1.75 (m, 2H), 1.92 (s, 3H), 1.94-2.02 (m, 2H), 2.13-2.18 (m, 2H), 3.60-3.76 (m, 3H), 6.84-6.97 (m, 1H), 7.04-7.24 (m, 5H), 7.36 (dd, J=8, 1 Hz, 1H), 7.45 (d, J=8 Hz, 1H). MS (ESI(+)) m/z 579 $(M+H)^+$. Anal calcd for

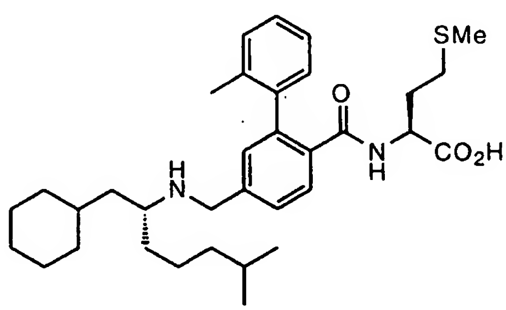
$C_{35}H_{49}N_2O_3SLi{\bullet}0.75H_2O$: C, 70.26; H, 8.51; N, 4.68. Found: C, 70.25; H, 8.52; N, 4.57.



Example 526

N-[4-N-(1-Cyclohexyl-6-methylhept-3-en-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 1.74-0.86 (m, 7H), 1.02-1.19 (m, 4H), 1.27-1.38 (m, 2H), 1.46-1.87 (m, 14H), 1.93 (s, 3H), 1.99 (s, 3H), 2.17 (m, 1H), 3.51-3.82 (m, 3H), 5.11 (m, 1H), 5.43 (m, 1H), 6.83-6.96 (m, 1H), 7.00-7.24 (m, 5H), 7.24-7.36 (m, 1H), 7.47 (d, J=7 Hz, 1H). MS (APCI(+)) m/z 565 $(M+H)^+$. Anal calcd for $C_{34}H_{47}N_2O_3SLi{\bullet}2.02H_2O$: C, 67.20; H, 8.48; N, 4.61. Found: C, 67.24; H, 8.35; N, 4.47.

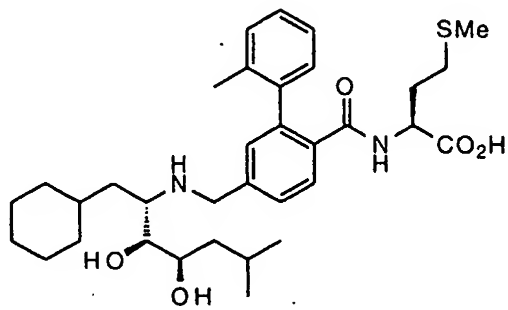


Example 527

N-[4-N-(1-Cyclohexyl-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 0.80 (d, J=5 Hz, 3H), 0.82 (d, J=5 Hz, 3H), 1.02-1.40 (m, 12H), 1.40-1.65 (m, 12H), 1.75-1.83 (m, 1H), 1.92 (s, 3H), 1.99 (m, 1H), 2.16 (m, 1H),

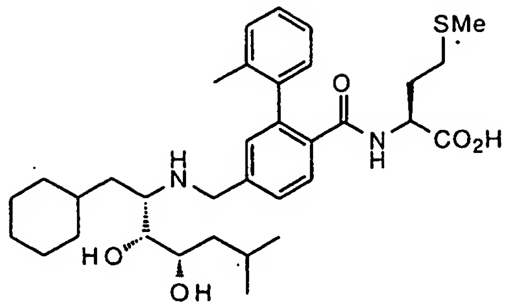
2.43 (m, 1H), 3.60-3.77 (m, 3H), 6.86-6.95 (m, 1H), 7.08-7.22 (m, 5H), 7.35 (d, J=8.0 Hz, 1H), 7.47 (d, J=8.0 Hz, 1H). MS (APCI(+)) m/z 567 $(M+H)^+$. Anal calcd for $C_{34}H_{49}N_2O_3SLi \cdot 1.15H_2O$: C, 66.99; H, 8.48; N, 4.60. Found: C, 67.03; H, 8.62; N, 4.49.



Example 528

N-[4-N-(1-Cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

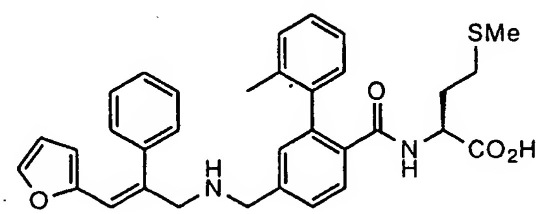
The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 0.72-1.35 (m, 10H), 0.85 (d, J=7 Hz, 3H), 0.87 (d, J=7 Hz, 3H), 1.43-1.76 (m, 6H), 1.82-2.14 (m, 4H), 2.00 (s, 3H), 2.06 (s, 3H), 3.07 (brs, 1H), 3.58 (s, 1H), 3.96-4.14 (m, 2H), 4.40-4.59 (m, 2H), 4.99-5.23 (m, 4H), 6.08-6.10 (m, 1H), 7.17-7.35 (m, 5H), 7.55 (m, 1H), 7.74 (m, 1H), 8.80 (brs, 0.5H), 9.25 (brs, 0.5H). MS (DCI/NH_3) m/z 599 $(M+H)^+$. Anal. calcd for $C_{34}H_{50}N_2O_5S \cdot 1.55H_2O \cdot 1.05TFA$: C, 55.70; H, 6.90; N, 3.51. Found: C, 55.72; H, 6.91; N, 3.38.



Example 529

N-[4-N-(1-Cyclohexyl-2,3-dihydroxy-6-methylheptan-2-yl) aminomethyl-2-(2-methylphenyl)benzoyl]methionine

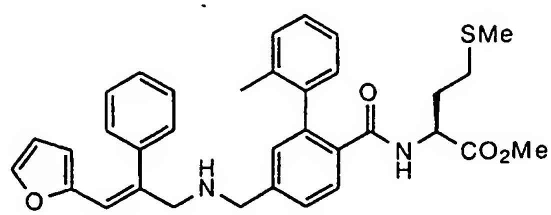
The desired compound was prepared according to the method of Example 158 ^1H NMR (300 MHz, DMSO) δ 0.80-1.40 (m, 16H), 1.45-1.77 (m, 6H), 2.00 (s, 3H), 2.04 (s, 3H), 1.80-2.13 (m, 4H), 3.20-3.40 (m, 1H), 3.59 (m, 1H), 3.39-4.10 (m, 1H), 4.38-4.55 (m, 1H), 4.60-4.90 (m, 4H), 6.10 (m, 1H), 7.20-7.40 (m, 5H), 7.55 (m, 1H), 7.80 (m, 1H), 9.0 (brs, 1H). MS (DCI/NH3) m/z 599 $(M+H)^+$. Anal calcd for $C_{34}H_{50}N_2O_5S \cdot 1.00H_2O \cdot 1.85TFA$: C, 54.70; H, 6.56; N, 3.38. Found: C, 54.70; H, 6.59; N, 3.27.



Example 537

N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

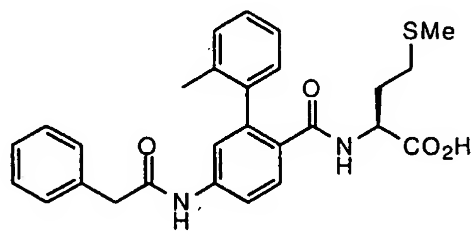
The desired compound was prepared according to the method of Examples158 ^1H NMR (MeOH-d_4) δ 7.69-7.61 (m, 1 H), 7.40-7.29 (m, 3 H), 7.22-7.17 (m, 9 H), 6.70 (dd, 1 H, J= 8.7, 2.6 Hz), 6.48 (bs, 1 H), 6.41-6.38 (m, 1 H), 6.15-6.13 (m, 1 H), 5.44 (d, 1 H, J= 3.4 Hz), 4.46-4.38 (m, 1 H), 4.10 (d, 2 H, J= 1.3 Hz), 2.18-1.85 (m, 8 H), 1.79-1.66 (m, 1 H), 1.59-1.52 (m, 1 H); MS m/z 541 (M^+ + 1, 100).



Example 538

N-[4-(3-furan-2-yl-2-phenylprop-2-en-1-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester

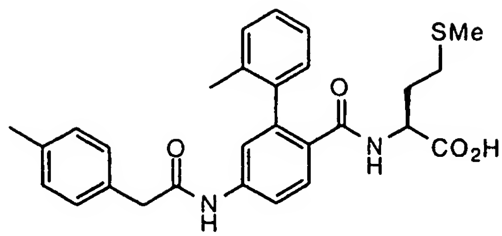
The desired compound was prepared according to the method of Example 158 ^{1}H NMR ($CDCl_3$) δ 7.93 (dd, 1 H, J= 17.7, 8.6 Hz), 7.42-7.27 (m, 6 H), 7.22-7.19 (m, 4 H), 6.67 (dd, 1 H, J= 8.8, 2.4 Hz), 6.52 (bs, 1 H), 6.33 (d, 1 H, J= 2.4 Hz), 6.15 (dd, 1 H, J= 3.4, 1.7 Hz), 5.70 (t, 1 H, J= 8.7 Hz), 5.52 (d, 1 H, J= 3.4 Hz), 4.62-4.55 (m, 1 H), 4.30-4.27 (m, 1 H), 4.14-4.11 (m, 2 H), 3.63 (s, 3 H), 2.18-2.00 (m, 8 H), 1.88-1.76 (m, 1 H), 1.56-1.48 (m, 1 H); MS m/z 555 (M^+ + 1, 100).



Example 540

N-[4-N-phenylacetylamino-2-(2-methylphenyl)benzoyl]methionine lithium salt

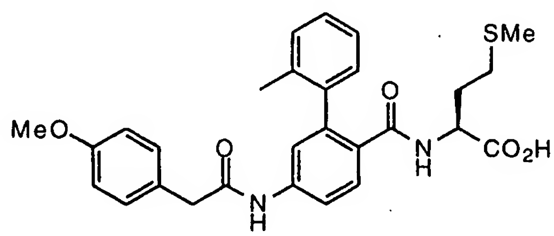
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (DMSO-d_6) δ 10.42 (s, 1 H), 7.60 (d, 1 H, J = 8.5 Hz), 7.51 (d, 1 H, J = 8.5 Hz), 7.47 (bs, 1 H), 7.34-7.28 (m, 3 H), 7.25-7.16 (m, 6 H), 6.97-6.85 (m, 1 H), 3.68-3.65 (m and s, 3 H total), 2.15-1.85 (m, 8 H), 1.78-1.64 (m, 1 H), 1.59-1.51 (m, 1 H); MS m/z 477 (M^+ + 1, 100).



Example 541

N-[4-N-(4'-methylphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

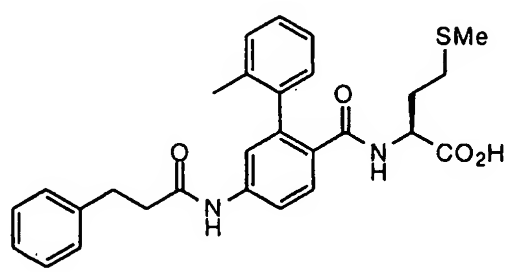
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (DMSO-d_6) δ 10.40 (s, 1 H), 7.60 (d, 1 H, J= 7.9 Hz), 7.51 (d, 1 H, J= 8.5 Hz), 7.46 (bs, 1 H), 7.22-6.83 (m, 9 H), 3.71-3.62 (m, 1 H), 3.60 (s, 2 H), 2.27 (s, 3 H), 2.23-1.86 (m, 8 H), 1.71-1.64 (m, 1 H), 1.60-1.52 (m, 1 H); MS m/z 491 (M+ + 1, 100).



Example 542

N-[4-N-(4'-methoxyphenylacetyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

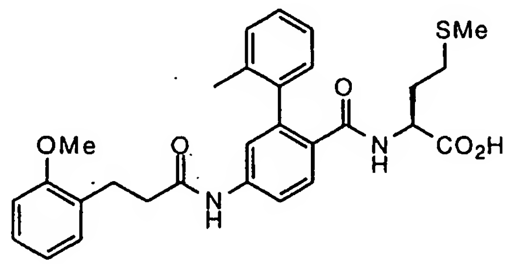
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (DMSO-d_6) δ 7.67-7.63 (m, 2 H), 7.50-7.45 (m, 1 H), 7.26-7.09 (m, 6 H), 6.89-6.85 (m, 2 H), 6.81-6.77 (m, 1 H), 4.24-4.20 (m, 1 H), 3.77 and 3.74 (2s, 3 H total), 3.62 and 3.39 (2s, 2 H total), 2.23-1.95 (m, 8 H), 1.89-1.78 (m, 1 H), 1.66-1.59 (m, 1 H); MS m/z 507 (M+ + 1, 100).



Example 543

N-[4-N-(3-phenylpropionoyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

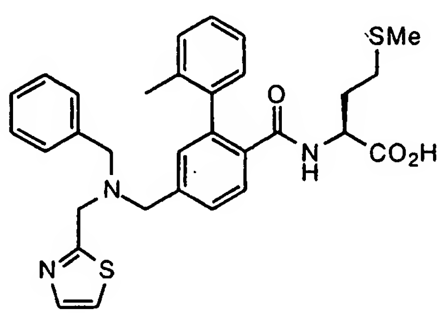
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (DMSO-d_6) δ 10.17 (bs, 1 H), 7.60 (d, 1 H, J= 7.9 Hz), 7.51 (d, 1 H, J= 8.6 Hz), 7.45 (bs, 1 H), 7.29-6.85 (m, 10 H), 3.71-3.65 (m, 1 H), 2.90 and 2.69 (2t, 2 H total, J= 7.9 Hz), 2.64 and 2.15 (2t, 2 H total, J= 7.9 Hz), 2.17-1.83 (m, 8 H), 1.71-1.64 (m, 1 H), 1.59-1.53 (m, 1 H); MS m/z 491 (M+ + 1, 100).



Example 544

N-[4-N-(3-(2-methoxyphenyl)propionoyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 57 ^{1}H NMR (DMSO-d_6) δ 10.10 (bs, 1 H), 7.59 (d, 1 H, J= 7.9 Hz), 7.50 (d, 1 H, J= 8.6 Hz), 7.45 (bs, 1 H), 7.22-7.09 (m, 6 H), 6.96 (d, 1 H, J= 7.9 Hz), 6.89-6.79 (m, 3 H), 3.78 and 3.76 (2s, 3 H total), 2.86 and 2.69 (2t, 2 H total, J= 7.9 Hz), 2.59 and 2.07 (2t, 2 H total, J= 7.9 Hz), 2.17-1.84 (m, 8 H), 2.71-2.63 (m, 1 H), 1.58-1.53 (m, 1 H); MS m/z 521 (M+ + 1, 100).

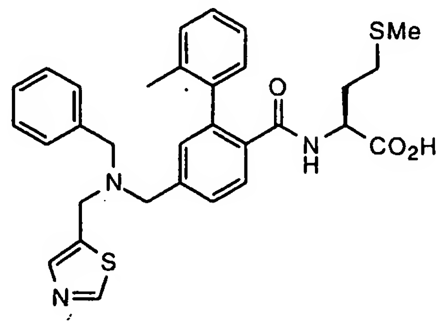


Example 548

N-[4-N-benzyl-N-(thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ^{1}H nmr (300 MHz, DMSO d_6): δ 8.09, d, 1H; 7.72, d, 1H; 7.66, d, 1H; 7.50, m, 2H; 7.38,

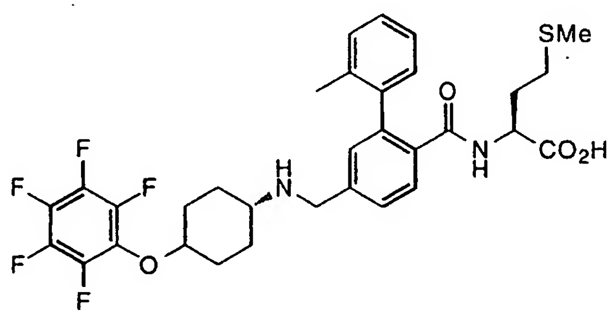
m, 4H; 7.23, m, 4H; 7.14, m, 2H; 4.20, ddd, 1H; 3.89, s, 2H; 3.70, s, 2H; 3.68, s, 2H; 2.09, m, 4H; 1.96, s, 3H; 1.63 - 1.90, m, 2H. MS (APCI(+)) 560 (MH+). Calc'd for $C_{31}H_{33}iN_3O_3S_2$•0.32 H_2O: C 65.84, H 6.00, N 7.43: Found: C 65.85, H 5.75, N 7.34



Example 549

N-[4-N-benzyl-N-(thiazol-5-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 158 ^1H nmr (300 MHz, DMSO d_6): δ 12.45, bs, 1H; 9.03, s, 1H; 8.12, d, 1H; 7.79, s, 1H; 7.48, dd, 2H; 7.35, m, 4H; 7.04 - 7.28, m, 6H4.21, ddd, 1H; 3.81, s, 2H; 3.61, s, 2H; 3.58, s, 1H; 1.98 - 2.21, 5H; 1.96, s, 3H; 1.61 - 1.89, m, 2H. MS (APCI(+)) 560 (MH+). Calc'd for $C_{31}H_{33}iN_3O_3S_2$•0.78 H_2O: C 64.89, H 6.07, N 7.32: Found: C 64.89, H 5.71, N 7.29

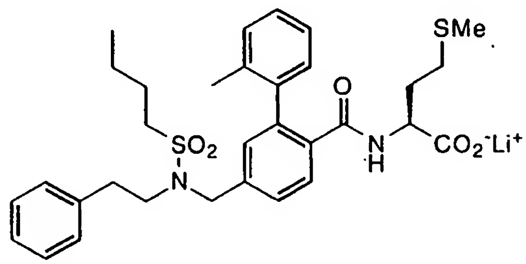


Example 596

N-[4-N-(4-*trans*-pentafluoropheynyloxycyclohexyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

A solution of *trans*-4-aminocylohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with *t*-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% $NaHCO_3$, and brine to give the Boc-

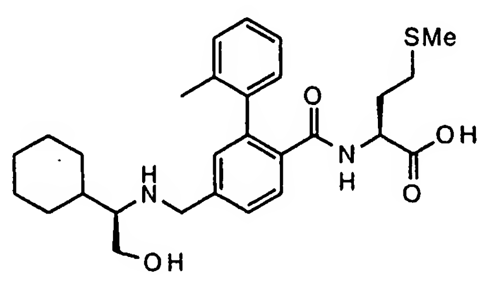
amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol) in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol was added and stirred overnight. Standard aqueous workup provided 149 mg of the protected pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped to dryness, and reductively alkylated and saponified in a manner analogous to Example 158 to provide 160 mg of the title compound. MS m/e 635 $(M-H)^-$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m, 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).



Example 598

N-[4-(*N*-2-phenethyl-*N*-butanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

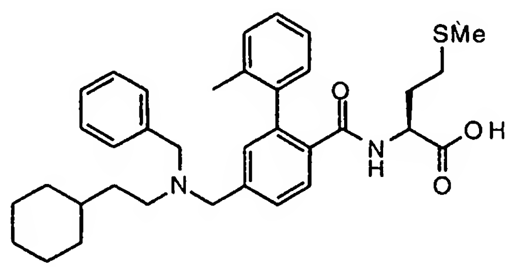
The desired compound was prepared according to the method of Example 157. ^1H (300MHz, DMSO-d6, δ) 7.62 (1H, d, J=7Hz), 7.52 (1H, dd, J=7&2Hz), 7.20-7.10 (10H, m), 7.14 (1H, bd, J=7Hz), 4.65 (2H, bs), 3.76 (1H, m), 3.00 (2H, m), 2.78 (2H, m), 2.25-2.00 (5H, m), 1.99 (3H, s), 1.90-1.70 (4H, m), 1.62 (2H, m), 1.37 (2H, m), 0.92 (3H, t, J=8Hz). m/e (ESI) 595 (MH^-) Anal.calc. for $C_{32}H_{39}LiN_2O_5S_2 \cdot 0.50\ H_2O$ C 62.83, H 6.59, N 4.38 Found C 62.59, H 6.59, N 4.44



Example 604

N-[4-(2-cyclohexylethan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

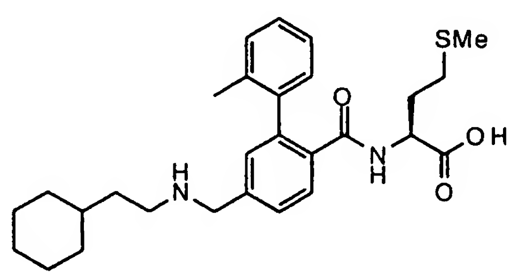
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 7.48 (d, *J*=8 Hz, 1H), 7.37 (dd, *J*=8, 1 Hz, 1H), 7.20-7.08 (m, 4H), 6.90 (m, 1H), 4.40 (t, *J*=5 Hz, 1H), 3.82-3.65 (m, 3H), 3.46 (m, 1H), 3.31 (m, 1H), 2.28-2.12 (m, 2H), 2.02-1.80 (m, 7H), 1.77-1.37 (m, 8H), 1.18-0.92 (m, 5H); Anal. Calcd for $C_{28}H_{37}LiN_2O_4S \cdot 1.35\ H_2O$: C, 63.58; H, 7.57; N, 5.30. Found: C, 63.55; H, 7.31; N, 4.89.



Example 605

N-[4-(N-benzyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

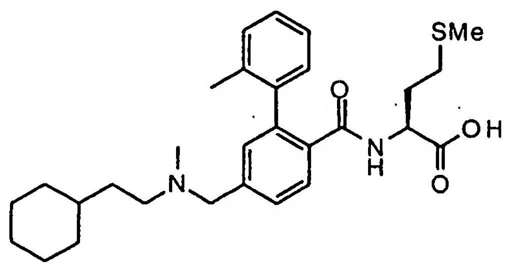
The desired compound was prepared according to the method of Example 158. MS (CI/NH$_3$) m/z: (M-H)$^-$ 571; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 7.50 (d, *J*=8 Hz, 1H), 7.38-7.12 (m, 10H), 6.92 (d, *J*=6 Hz, 1H), 3.69 (m, 1H), 3.56 (s, 2H), 3.53 (s, 2H), 2.38 (t, *J*=7 Hz, 2H), 2.15-1.95 (m, 4H), 1.91 (s, 3H), 1.58-1.42 (m, 7H), 1.38-1.02 (m, 7H), 0.81-0.68 (m, 2H); Anal. Calcd for $C_{35}H_{43}LiN_2O_3S \cdot 1.75\ H_2O$: C, 68.89; H, 7.68; N, 4.59. Found: C, 68.85; H, 7.44; N, 4.37.



Example 607

N-[4-(N-2-cyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Trifluoroacetate Salt

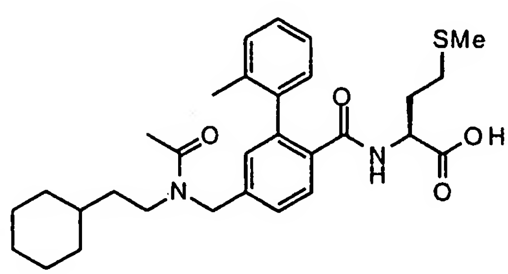
The desired compound was prepared according to the method of Example 158. MS (CI/NH3) m/z: $(M+H)^+$ 483; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.09 (m, 1H), 7.49-7.42 (m, 2H), 7.26 (m, 1H), 7.16-6.98 (m, 3H), 4.14 (m, 1H), 4.11 (s, 2H), 2.87-2.80 (m, 2H), 2.11-1.90 (m, 5H), 1.86 (s, 3H), 1.78-1.47 (m, 7H), 1.45-1.37 (m, 2H), 1.26-1.00 (m, 4H), 0.87-0.72 (m, 2H); Anal. Calcd for $C_{28}H_{38}N_2O_3S{\bullet}C_2HF_3O_2{\bullet}1.45\ H_2O$: C, 57.76; H, 6.93; N, 4.49. Found: C, 57.69; H, 6.51; N, 4.48.



Example 608

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

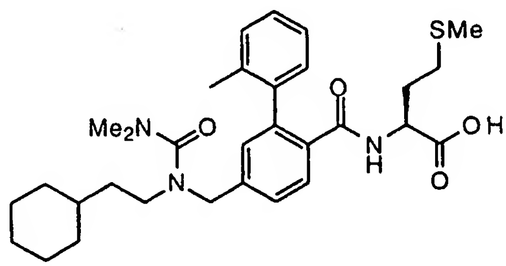
The desired compound was prepared according to the method of Example 158. MS (CI/NH3) m/z: $(M+H)^+$ 497; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.49 (d, J=8 Hz, 1H), 7.32 (dd, J=8, 1 Hz, 1H), 7.25-7.06 (m, 4H), 6.93 (d, J=6 Hz, 1H), 3.73-3.64 (m, 1H), 3.49 (s, 2H), 2.32 (t, J=7 Hz, 2H), 2.15 (m, 1H), 2.12 (s, 3H), 2.06-1.80 (m, 3H), 1.92 (s, 3H), 1.74-1.50 (m, 7H), 1.35-1.05 (m, 7H), 0.90-0.76 (m, 2H); Anal. Calcd for $C_{29}H_{39}LiN_2O_3S{\bullet}1.05\ H_2O$: C, 66.78; H, 7.94; N, 5.37. Found: C, 66.81; H, 7.75; N, 5.07.



Example 609

N-[4-(N-acetyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

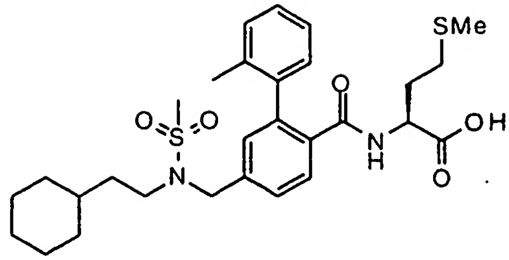
The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with acetic anhydride - lithium carbonate under Schotten-Baumann conditions. MS (CI/NH_3) m/z: $(M-H)^-$ 523; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.59 minor conformer 7.53 major conformer (d, J=8 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 7.25-7.14 (m, 3H), 7.07-6.96 (m, 2H), 4.63 minor conformer 4.57 major conformer (s, 2H), 3.80 (m, 1H), 3.33-3.25 (m, 2H), 2.21-1.85 (m, 10H), 1.77-1.56 (m, 7H), 1.44-1.30 (m, 3H), 1.25-1.07 (m, 4H), 0.95-0.83 (m, 2H); Anal. Calcd for $C_{30}H_{39}LiN_2O_4S \cdot 1.45\ H_2O$: C, 64.72; H, 7.59; N, 5.03. Found: C, 64.75; H, 7.40; N, 4.71.



Example 610

N-[4-(N-(N,N-dimethylaminocarbonyl)-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

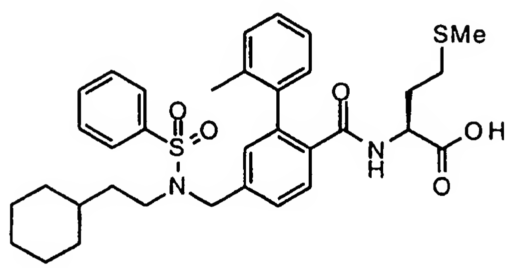
The compound resulting from Example 607 was treated with dimethyl carbamoyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH_3) m/z: $(M+H)^+$ 554; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.18 (d, J=8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 2 Hz, 1H), 7.29-7.13 (m, 4H), 4.40 (s, 2H), 4.28 (m, 1H), 3.13-3.06 (m, 2H), 2.80 (s, 6H), 2.29-2.06 (m, 5H), 2.02 (m, 3H), 1.94-1.62 (m, 6H), 1.47-1.15 (m, 7H), 0.96-0.84 (m, 2H); Anal. Calcd for $C_{31}H_{43}N_3O_4S \cdot 0.45\ H_2O$: C, 66.27; H, 7.88; N, 7.48. Found: C, 66.37; H, 8.10; N, 6.88.



Example 611

N-[4-(N-(2-cyclohexylethyl)-N-methanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

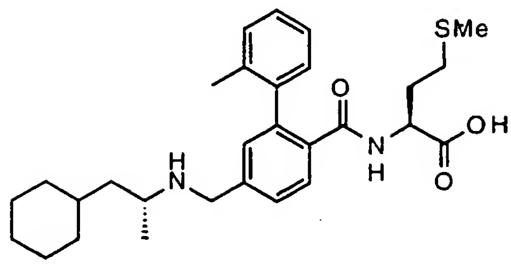
The compound resulting from Example 607 was treated with methanesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH_3) m/z: $(M-H)^-$ 559; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.54 (d, J=8 Hz, 1H), 7.41 (d, J=8 Hz, 1H), 7.25-7.13 (m, 4H), 6.97 (d, J=7 Hz, 1H), 4.36 (s, 2H), 3.67 (m, 1H), 3.17-3.12 (m, 2H), 2.96 (s, 3H), 2.17-1.91 (m, 6H), 1.70-1.48 (m, 9H), 1.31-1.04 (m. 6H), 0.82-0.69 (m, 2H); Anal. Calcd for $C_{29}H_{39}LiN_2O_5S_2$•2.75 H_2O: C, 56.52; H, 7.28; N, 4.55. Found: C, 56.72; H, 6.49; N, 3.92.



Example 612

N-[4-(N-benzenenesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

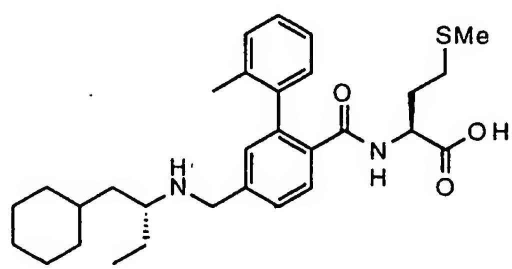
The compound resulting from Example 607 was treated with benzenesulfonyl chloride under Schotten-Baumann conditions to yield the title compound. MS (CI/NH_3) m/z: $(M-H)^-$ 621; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.86 (m, 1H), 7.72-7.59 (m, 4H), 7.51 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.26-7.07 (m, 4H), 6.96 (d, J=6 Hz, 1H), 4.36 (s, 2H), 3.66 (m, 1H), 3.10 (m, 2H), 2.16-1.92 (m, 5H), 1.70-1.40 (m, 7H), 1.30-0.99 (m, 6H), 0.90-0.61 (m, 5H); Anal. Calcd for $C_{34}H_{41}LiN_2O_5S_2$•1.25 H_2O: C, 62.70; H, 6.73; N, 4.30. Found: 63.10; H, 6.72; N, 3.52.



Example 613

N-[4-(3-cyclohexylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

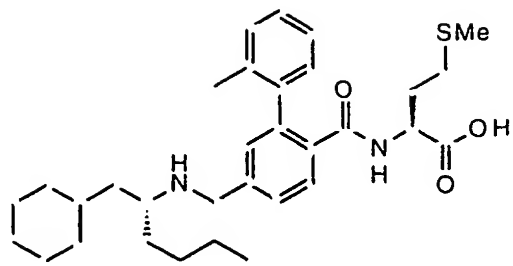
The desired compound was prepared according to the method of Example 158 MS (CI/NH_3) m/z: $(M+H)^+$ 497; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.63 (m, 1H), 7.52-7.43 (m, 2H), 7.25-7.04 (m, 4H), 4.06 (m, 1H), 3.97 (d, J=14 Hz, 1H), 3.89 (d, J=14 Hz, 1H), 2.85 (m, 1H), 2.17-1.94 (m, 5H), 1.94 (s, 3H), 1.84-1.52 (m, 7H), 1.50-1.02 (m, 9H), 0.90-0.77 (m, 2H); Anal. Calcd for $C_{29}H_{40}N_2O_3S$•1.55 H_2O: C, 66.39; H, 8.28; N, 5.34. Found: 66.39; H, 7.89; N, 5.11.



Example 614

N-[4-(4-cyclohexylbutan-3-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

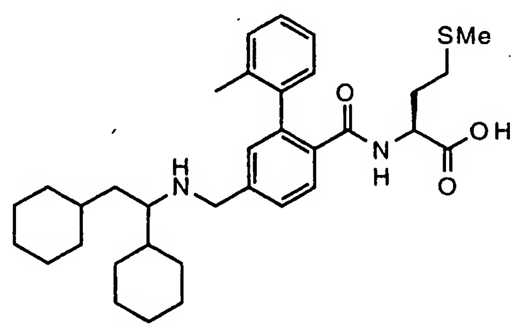
The desired compound was prepared according to the method of Example 158 MS (CI/NH_3) m/z: $(M+H)^+$ 511; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.48 (d, J=8 Hz, 1H), 7.36 (d, J=6 Hz, 1H), 7.25-7.09 (m, 4H), 7.00-6.85 m, 1H), 3.80-3.65 (m, 3H), 2.42 (m, 1H), 2.20-1.50 (m, 15H), 1.41-1.06 (m, 8H), 0.90-0.70 (m, 2H), 0.79 (t, J=7 Hz, 3H); Anal. Calcd for $C_{30}H_{41}LiN_2O_3S$•1.25 H_2O: C, 66.83; H, 8.13; N, 5.20. Found: 66.86; H, 7.91; N, 4.93.



Example 615

N-[4-(6-cyclohexylhexan-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

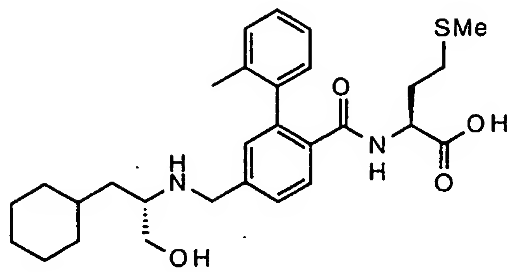
The desired compound was prepared according to the method of Example 158 MS (CI/NH_3) m/z: $(M-H)^-$ 537; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (dd, J=8, 1 Hz, 1H), 7.24-7.07 (m, 4H), 6.90 (m, 1H), 3.75-3.62 (m, 3H), 2.45 (m, 1H), 2.18-1.50 (m, 15H), 1.40-1.07 (m, 12H), 0.88-0.75 (m, 5H); Anal. Calcd for $C_{32}H_{45}LiN_2O_3S$•1.05 H_2O: C, 68.19; H, 8.42; N, 4.97. Found: 68.19; H, 8.25; N, 4.77.



Example 616

N-[4-(1,2-dicyclohexylethylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

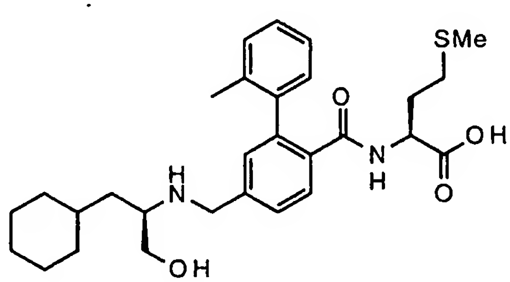
The desired compound was prepared according to the method of Example 158 MS (CI/NH_3) m/z: $(M+H)^+$ 565; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.36 (m, 1H), 7.23-7.12 (m, 4H), 6.91 (m, 1H), 3.77-3.63 (m, 3H), 2.30 (m, 1H), 2.15 (m, 1H), 2.03-1.85 (m, 6H), 1.80-1.40 (m, 12H), 1.30-0.65 (m, 15H); Anal. Calcd for $C_{34}H_{47}LiN_2O_3S$•2.25 MeOH: C, 67.05; H, 8.15; N, 4.60. Found: 67.37; H, 7.69; N, 4.46.



Example 617

N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

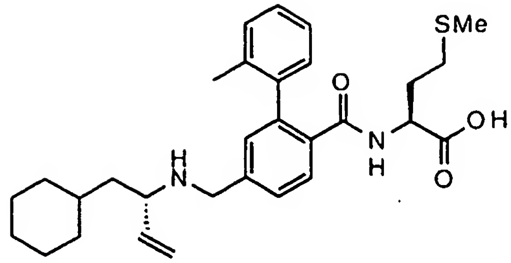
The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: $(M+H)^+$ 513; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, *J*=7 Hz, 1H), 7.42 (d, *J*=7 Hz, 1H), 7.23-7.05 (m, 4H), 4..18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for $C_{29}H_{40}N_2O_4S$•1.65 H_2O: C, 64.21; H, 8.05; N, 5.16. Found: 64.26; H, 7.64; N, 4.77.



Example 618

N-[4-(3-cyclohexylpropan-1-ol-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Trifluoroacetate Salt

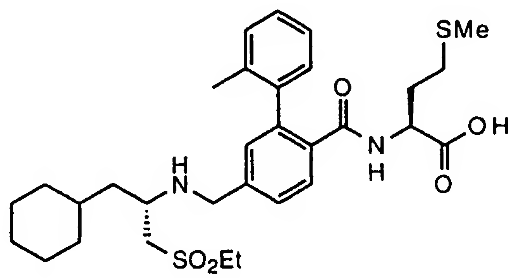
The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: $(M+H)^+$ 513; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.85 (m, 1H), 7.49 (d, *J*=7 Hz, 1H), 7.42 (d, *J*=7 Hz, 1H), 7.23-7.05 (m, 4H), 4..18-4.12 (m, 2H), 3.92-3.84 (m, 2H), 3.45 (m, 1H), 2.65 (m, 1H), 2.18-2.00 (m, 4H), 1.85-1.55 (m, 6H), 1.38-1.08 (m, 10 H), 0.89-0.77 (m, 3H); Anal. Calcd for $C_{29}H_{40}N_2O_4S$•$C_2HF_3O_2$•1.70 H_2O: C, 56.64; H, 6.81; N, 4.26. Found: 56.67; H, 6.89; N, 4.11.



Example 619

N-[4-(2-cyclohexylprop-1-en-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

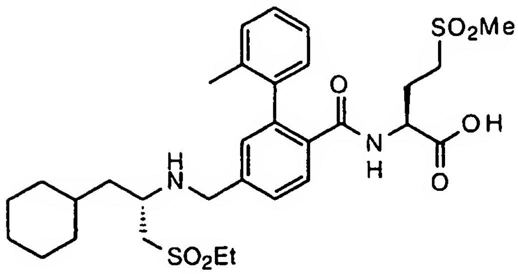
The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: (M-H)$^-$ 507; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 7.47 (d, J=8 Hz, 1H), 7.32 (m, 1H), 7.25-7.07 (m, 4H), 6.93 (m, 1H), 5.52 (ddd, J=17, 10, 8 Hz, 1H), 5.05 (dd, J=10, 2 Hz, 1H), 4.97 (dd, J=17, 2 Hz, 1H), 3.77 (d, J=15 Hz, 1H), 3.70 (m, 1H), 3.57 (d, J=15 Hz, 1H), 2.94 (m, 1H), 2.17-1.50 (m, 15H), 1.38-1.06 (m, 6H), 0.90-0.77 (m, 2H); Anal. Calcd for $C_{30}H_{39}LiN_2O_3S$•1.90 H_2O: C, 65.65; H, 7.86; N, 5.10. Found: 65.64; H, 7.34; N, 4.80.



Example 620

N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

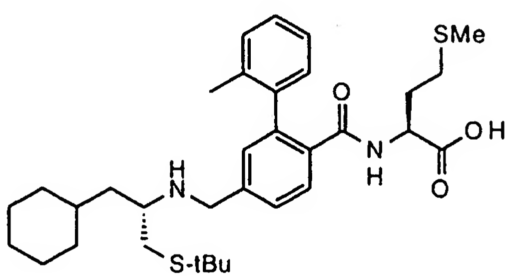
The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: (M+H)$^+$589; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 7.52 (d, J=8 Hz, 1H), 7.38 (dd, J=8, 1 Hz, 1H), 7.27-7.10 (m, 4H), 6.97 (m, 1H), 3.83-3.68 (m, 3H), 3.33 (m, 1H), 3.20-3.07 (m, 3H), 2.97 (dd, J=14, 5Hz, 1H), 2.28-1.81 (m, 8H), 1.78-1.08 (m, 16H), 0.92-0.75 (m, 2H); Anal. Calcd for $C_{31}H_{43}LiN_2O_5S_2$•4.25 H_2O: C, 55.46; H, 7.73; N, 4.17. Found: 55.43; H, 6.94; N, 4.03.



Example 621

N-[4-(3-cyclohexyl-1-ethylsulfonylpropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]-2-amino-4-methanesulfonylbutanoic acid Lithium Salt

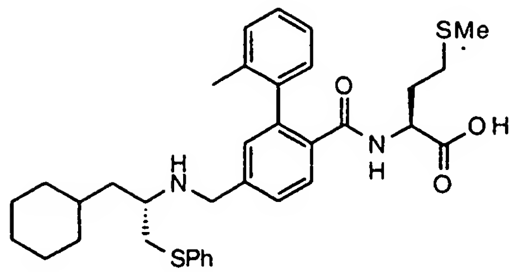
The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: $(M-H)^{-}$619; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.53 (d, J=8 Hz, 1H), 7.37 (d, J=8 Hz, 1H), 7.25-7.09 (m, 4H), 6.97 (m, 1H), 3.78-3.65 (m, 3H), 3.25 (m, 1H), 3.21-2.91 (m, 4H), 2.80 (s, 3H), 2.28-1.07 (m, 21H), 0.92-0.84 (m, 2H); Anal. Calcd for $C_{31}H_{43}LiN_2O_7S_2$•1.25 H_2O: C, 57.35; H, 7.06; N, 4.31. Found: 57.35; H, 7.03; N, 4.11.



Example 622

N-[4-(3-cyclohexyl-1-t-butylthiopropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH3) m/z: $(M+H)^{+}$584; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.7.47 (d, J=8 Hz, 1H), 7.37 (dd, J=8, 1 Hz, 1H), 7.23-7.13 (m, 4H), 6.97 (m, 1H), 3.87-3.72 (m, 2H), 3.65 (m, 1H), 2.63 (m, 1H), 2.18-1.77 (m, 8H), 1.74-1.00 (m, 24 H), 0.91-0.68 (m, 2H); Anal. Calcd for $C_{33}H_{47}LiN_2O_3S_2$•4.50 EtOH: C, 59.39; H, 7.78; N, 4.70. Found: 59.65; H, 7.43; N, 3.91.



Example 623

N-[4-(3-cyclohexyl-1-phenylthiopropan-2-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine Lithium Salt

The desired compound was prepared according to the method of Example 158 MS (CI/NH_3) m/z: $(M+H)^+$605; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.7.46 (d, J=8 Hz, 1H), 7.34-6.85 (m, 11H), 3.86-3.65 (m, 3H), 3.11 (dd, J=13, 5 Hz, 1H), 2.87 (m, 1H), 2.67 (m, 1H), 2.17-0.60 (m, 23H); Anal. Calcd for $C_{35}H_{43}LiN_2O_3S_2 \cdot 1.20\ H_2O$: C, 66.47; H, 7.24; N, 4.43. Found: 66.43; H, 7.27; N, 4.49.

Examples 626-668 and Examples 669-758

Compounds 626-667, 669-722, and 723-727 were synthezised by reductive amination of the compound described in Example 625, by the procedure described in Example 158

R_1 = Ph

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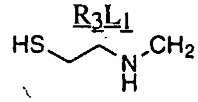
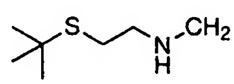
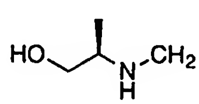
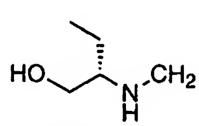
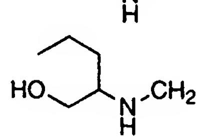
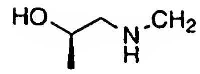
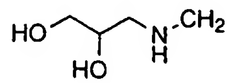
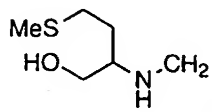
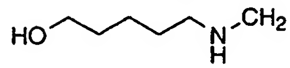
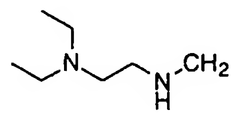
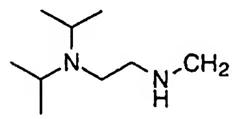
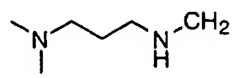
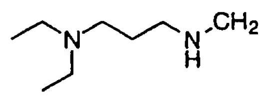
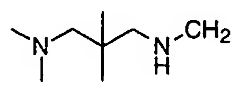
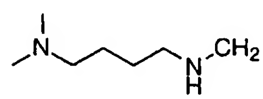
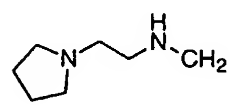
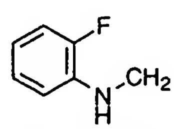
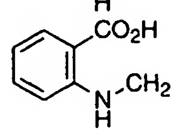
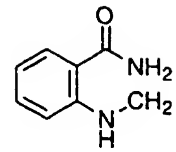
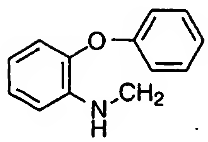
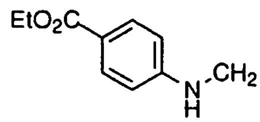
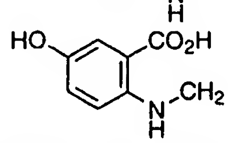
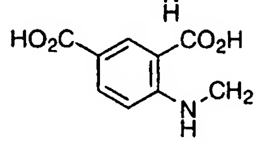
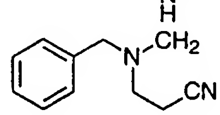
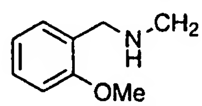
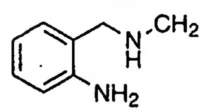
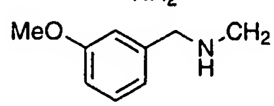
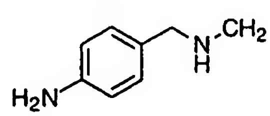
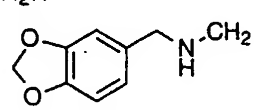
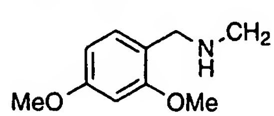
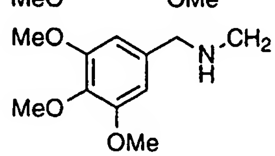
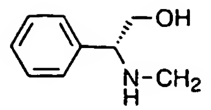
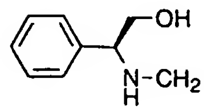
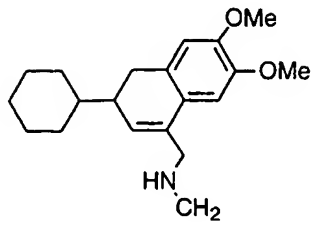
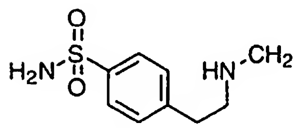
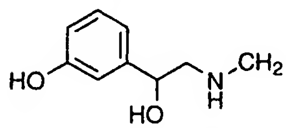
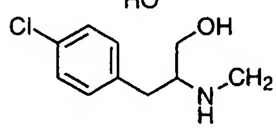
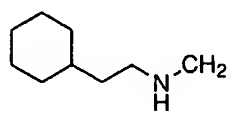
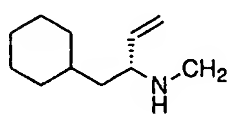
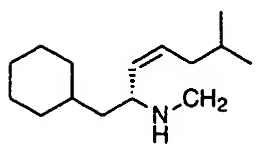
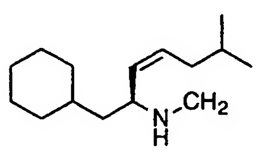
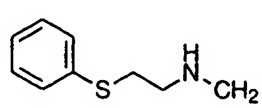
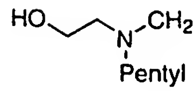
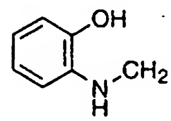
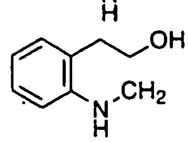
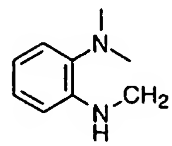
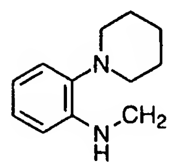
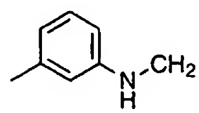
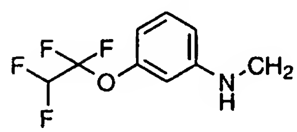
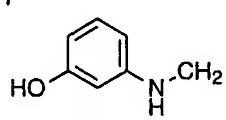
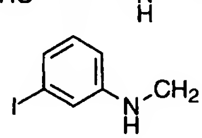
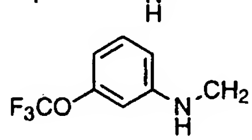
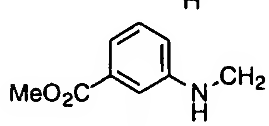
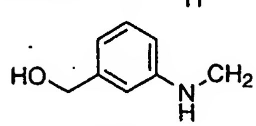
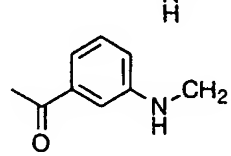
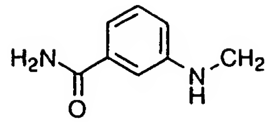
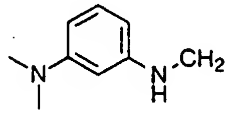
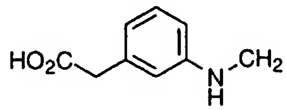
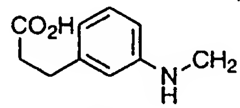
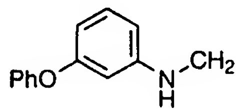
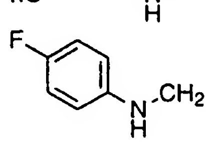
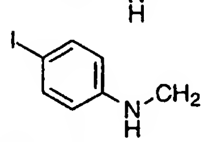
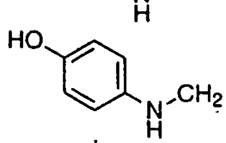
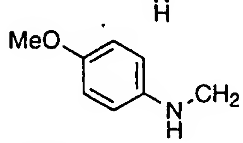
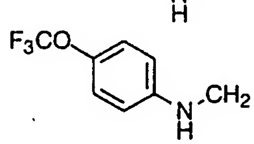
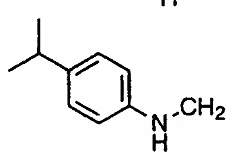
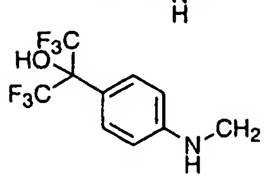
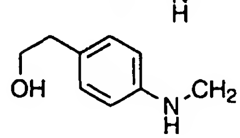
626		419
627		475
628		417
629		431
630		445

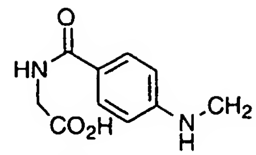
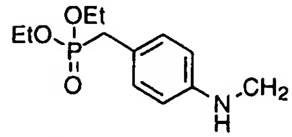
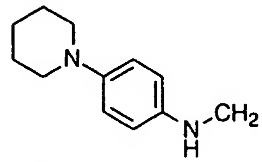
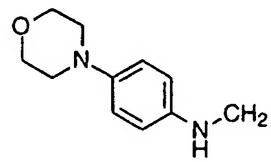
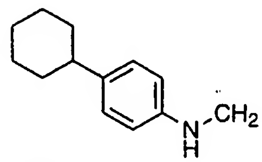
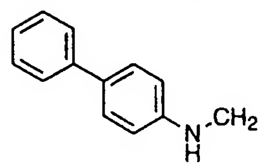
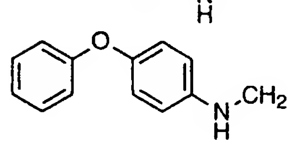
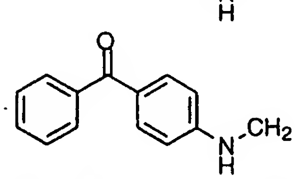
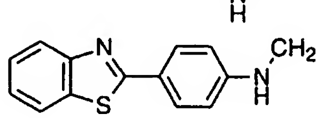
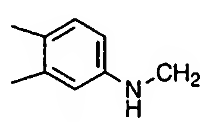
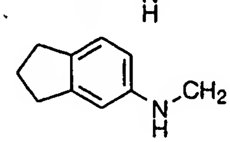
631		417
632		433
633		477
634		445
635		458
636		486
637		444
638		472
639		472
640		458
641		456
642		453
643		479

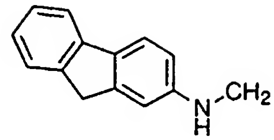
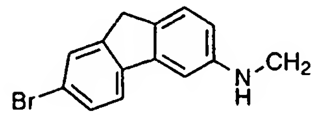
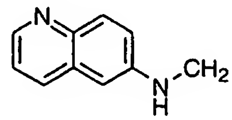
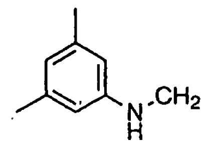
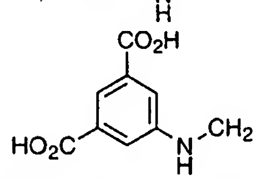
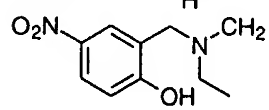
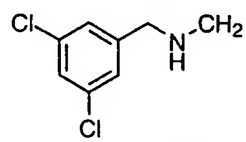
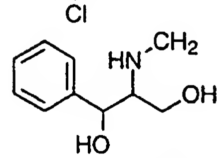
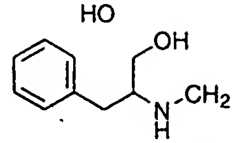
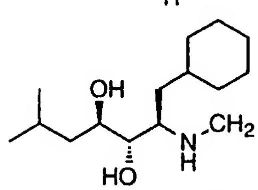
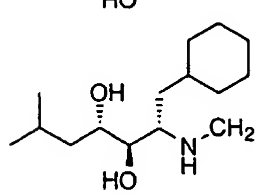
644		478
645		527
646		507
647		495
648		459
649		502
650		479
651		450
652		479
653		464
654		493
655		509
656		539

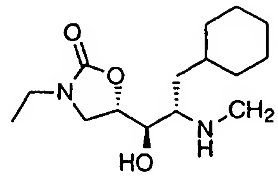
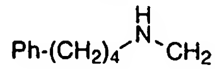
657		479
658		479
659		643
660		542
661		495
662		527
663		469
664		495
665		551
666		551
667		495

669		457
670		435
671		479
672		478
673		518
674		449
675		551
676		451
677		561
678		519
679		493
680		465
681		477

682		478
683		478
684		493
685		507
686		527
687		453
688		561
689		451
690		465
691		519
692		477
693		601
694		479

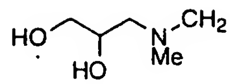
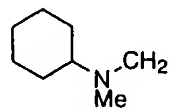
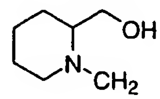
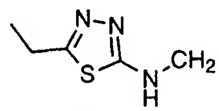
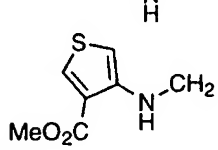
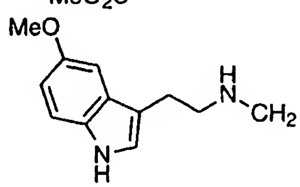
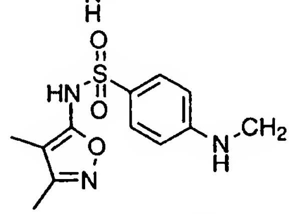
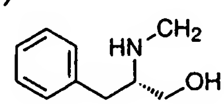
695		536
696		585
697		518
698		520
699		517
700		511
701		527
702		539
703		568
704		463
705		475

706		523
707		601
708		486
709		463
710		523
711		538
712		517
713		509
714		493
715		585
716		585

717		601
718		491

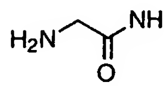
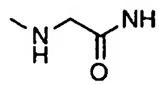
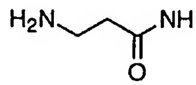
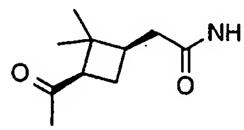
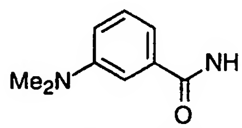
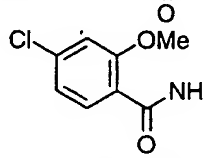
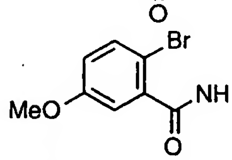
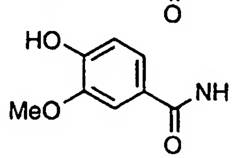
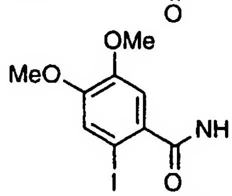
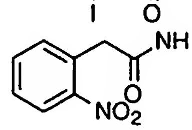
$R_1 = 2\text{-}MeC_6H_4\text{-}$

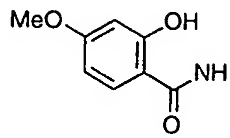
8265

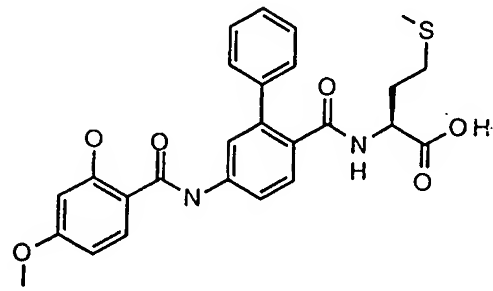
Example	R_3L_1	MS $(M+H)^+$
719		461
720		459
721		483
723		485
724		513
725		549
726		623
727		506

Examples 748-758 were prepared by the procedure described in Example 57

$R_1 = Ph$

Example	R_3L_1	MS $(M+H)^+$
748		402
749		416
750		416
751		511
752		492
753		513
754		558
755		489
756		635
757		508

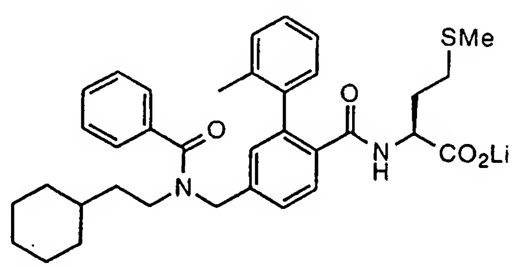
758  489



Example 759

(2S)-2-*N*-[4-(*N*-benzyl-*N*-3-pyridylaminomethyl)-2-(2-methylphenyl)benzoyl]amino-4-methanesulfonylbutanoic acid .

The desired compound was prepared according to the method of Example 157. [1]H (300 MHz., DMSO d_6): δ 12.8, (1H, s), 8.18, (1H, d J=8.Hz), 7.50 (2H, d, J=8Hz), 7.38 - 7.09 (14H, m), 4.83 (2H, s), 4.78 (2H, s), 4.21 (1H, s), 2.91 (3H, s), 2.76 (1H, m), 2.02, (1H, m), 2.00, (3H, s), 1.85 (2H, m). MS (DCI - NH_3) *m/z* 572 (MH+); Anal calcd for $C_{32}H_{33}N_3O_5 \cdot 1H_2O$: C, 65.18. H, 5.98. N, 7.13 Found: C, 65.54; H, 5.73; N, 6.82.

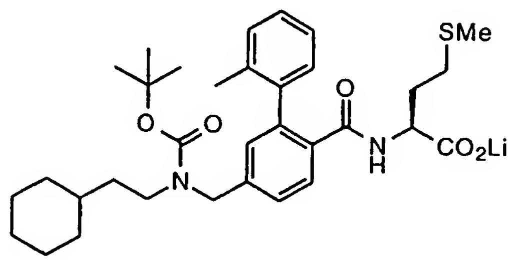


Example 762

N-[4-*N*-Benzoyl-*N*-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with benzoyl chloride - lithium carbonate under Schotten-Baumann conditions. MS (CI/NH_3) m/z: $(M-H)^-$ 585; [1]H NMR (DMSO-d_6, 300 MHz) δ 7.53 (m, 1H), 7.45-7.32 (m, 6H), 7.25-7.08 (m, 4H), 6.94 (m, 1H), 4.73-4.68 (m, 2H),

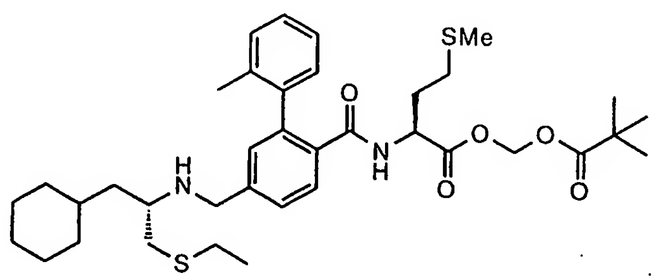
3.67-3.61 (m, 1H), 3.18-3.10 (m, 2H), 2.17-1.94 (m, 7H), 1.70-1.15 (m, 14H), 0.68-0.55 (m, 2H); Anal. Calcd for $C_{35}H_{41}LiN_2O_4S{\bullet}1.80\ H_2O$: C, 67.25; H, 7.19; N, 4.48. Found: C, 67.23; H, 6.78; N, 4.28.



Example 763

N-[4-*N*-t-Butyloxycarbonyl-*N*-2-cyclohexylethylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 607. The resultant amine was reacted with di-t-butyl dicarbonate under Schotten-Baumann conditions. MS (CI/NH_3) m/z: $(M-H)^-$ 581; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.51 (m, 1H), 7.31-6.93 (m, 6H), 4.41 (s, 2H), 3.69-3.61 (m, 1H), 3.25-3.13 (m, 2H), 2.14 (m, 1H), 2.02-1.91 (m, 2H), 1.91 (s, 3H), 1.66-1.51 (m, 8H), 1.45-1.05 (m, 16H), 0.88-0.75 (m, 2H); Anal. Calcd for $C_{23}H_{45}LiN_2O_5S{\bullet}1.70\ H_2O$: C, 64.00; H, 7.88; N, 4.52. Found: C, 63.99; H, 7.49; N, 4.33.

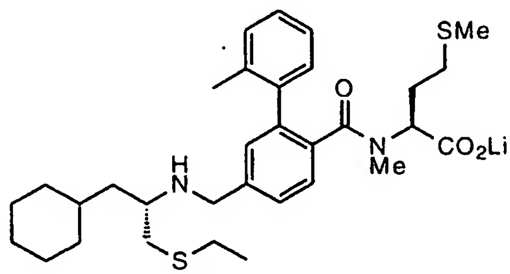


Example 764

Pivaloyloxymethyl *N*-[4-*N*-(3-Cyclohexyl-1-ethylthiopropan-2-yl)-*N*-methylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine hydrochloride salt

The desired compound was prepared by reaction of the compound resulting from Example 763 under conditions described in Example 500, followed by treatment with 4N HCl - dioxane. MS (CI/NH_3) m/z: $(M+H)^+$ 671; ^1H NMR (DMSO-d_6, 300 MHz) δ 8.42 (d, J=7.5 Hz, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.5 Hz, 1H), 7.49-7.42 (m, 1H),

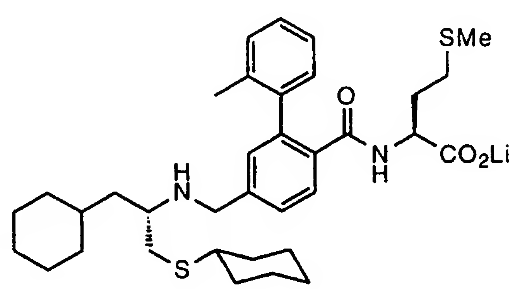
7.26-7.06 (m, 3H), 5.73 (d, J=5.8 Hz, 1H), 5.65 (d, J=5.8 Hz, 1H), 4.29 (brs, 2H), 3.25-3.17 (m, 1H), 3.04-2.97 (m, 1H), 2.86-2.77 (m, 1H), 2.24-2.02 (m, 6H), 1.94 (s, 3H), 1.83-1.40 (m, 12H), 1.25-1.07 (m, 6H), 1.13 (s, 9H), 0.93-0.77 (m, 2H); Anal. Calcd for $C_{37}H_{55}ClN_2O_5S_2$: C, 62.82; H, 7.84; N, 3.96. Found: C, 62.71; H, 8.03; N, 3.90.



Example 765

N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropan-2-yl)-*N*-methylaminomethyl-2-(2-methylphenyl)benzoyl]-*N*-methylmethionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH3) m/z: $(M-H)^-$ 569; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.38 (d, J=7.8 Hz, 1H), 7.24-7.04 (m, 6H), 4.53-4.45 (m, 1H), 3.85-3.67 (m, 2H), 2.67-2.59 (m, 2H), 2.50-2.38 (m, 5H), 2.18-1.92 (m, 5H), 1.87 (s, 3H), 1.70-1.05 (m, 17H), 0.93-0.72 (m, 2H); Anal. Calcd for $C_{32}H_{45}LiN_2O_3S_2 \cdot 1.20\ H_2O$: C, 64.23; H, 7.98; N, 4.68. Found: C, 64.27; H, 7.97; N, 4.66.

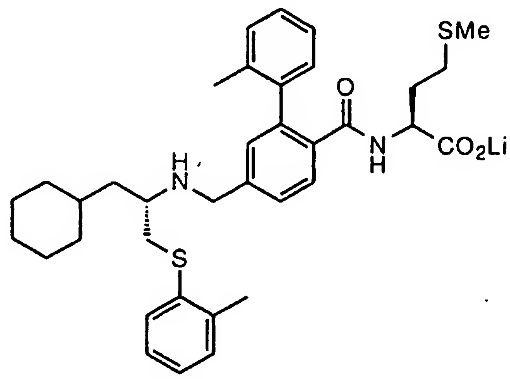


Example 766

N-[4-*N*-(3-Cyclohexyl-1-cyclohexylthiopropan-2-yl)-*N*-methylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH3) m/z: $(M-H)^-$ 609; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.48 (d, J=7.7 Hz, 1H), 7.34 (m, 1H), 7.21-7.06 (m, 4H), 6.96-6.88 (m, 1H), 3.83-3.66 (m, 3H), 2.64-2.54 (m,

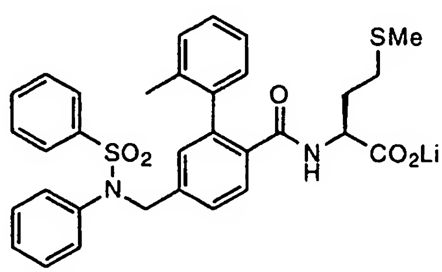
2H), 2.15-1.90 (m, 4H), 1.90 (s, 3H), 1.87-1.02 (m, 26H), 0.87-0.75 (m, 2H); Anal. Calcd for $C_{35}H_{49}LiN_2O_3S_2$•1.05 H_2O•1.60 TFA: C, 56.08; H, 6.49; N, 3.42. Found: C, 56.05; H, 6.50; N, 3.49.



Example 767

N-[4-N-(3-Cyclohexyl-1-(2-methylphenyl)thiopropan-2-yl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 158. MS (CI/NH_3) m/z: $(M-H)^-$ 617; ^1H NMR (DMSO-d_6, 300 MHz) δ 7.45 (d, J=7.8 Hz, 1H), 7.32-6.85 (m, 10H), 3.82-3.64 (m, 3H), 3.06 (dd, J=12.5, 4.4 Hz, 1H), 2.88-2.78 (m, 1H), 2.74-2.62 (m, 1H), 2.23 (s, 3H), 2.16-2.08 (m, 2H), 1.97-1.90 (m, 2H), 1.92 (s, 3H), 1.85-0.98 (m, 14H), 0.90-0.63 (m, 2H); Anal. Calcd for $C_{36}H_{45}LiN_2O_3S_2$•1.0 H_2O: C, 67.16; H, 7.51; N, 4.35. Found: C, 67.17; H, 7.30; N, 4.24.

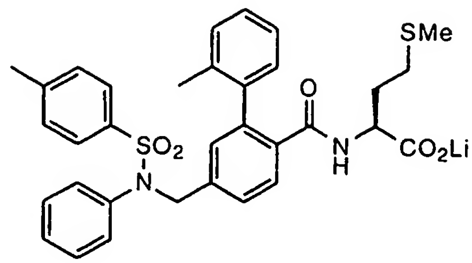


Example 769

N-[4-N-(N-phenyl-N-benzenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ^1H(CD_3OD): δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m);

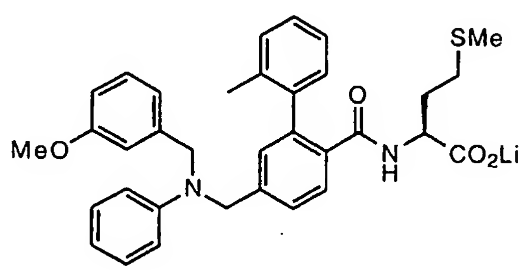
6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.1-1.5 (10H, m). ESI(-)/MS: 587(M-Li); 407.



Example 770

N-[4-N-(N-phenyl-N-toluenesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

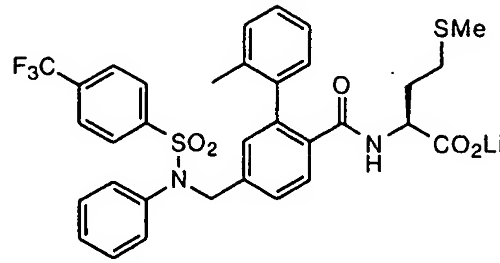
The desired compound was prepared according to the method of Example 157. $^1H(CD_3OD)$: δ 7.6-7.7 (2H, m); 7.5-7.6 (2H, m); 7.3-7.4 (1H, m); 7.3-7.1 (10H, m); 6.9-7.1 (2H, m); 4.9 (2H, s); 4.1-4.3 (1H, m); 2.4 (3H, m); 1.5-2.1 (10H, m). ESI(-)/MS: 601(M-Li); 421



Example 779

N-[4-N-(N-phenyl-N-(3-methoxybenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

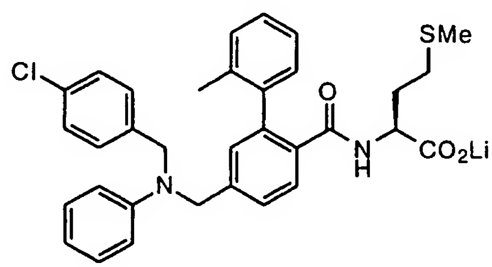
The desired compound was prepared according to the method of Example 157. $^1H(MeOH\text{-}d_4)$: δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.0-7.3 (8H, m); 6.6-6.85 (6H, m); 4.7 (2H, s); 4.65 (2H, s); 4.18-4.3 (1H, m); 3.65 (3H, s); 1.5-2.2 (10H, m). ESI(-)/MS: 567(M-Li); 447; 366; 281.



Example 780

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzenesulfonyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

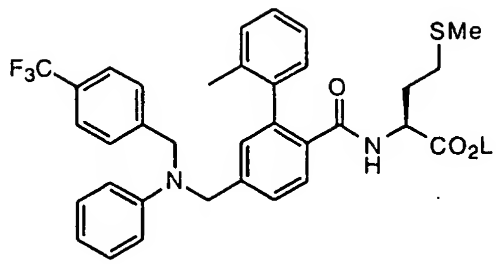
The desired compound was prepared according to the method of Example 157. $^{1}H(MeOH\text{-}d_4)$: δ 7.8-7.95 (4H, m); 7.5-7.6 (1H, d), 7.3-7.4 (1H, d); 7.1-7.3 (7H, m); 6.95-7.1 (3H, m); 4.9 (2H, s); 4.1-4.22 (1H, m); 1.7-2.1 (10H, m); 1.5-1.7 (1H, m). ESI(-)/MS: 655(M-Li); 475. 431.



Example 781

N-[4-N-(N-phenyl-N-(4-chlorobenzyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. $^{1}H(MeOH\text{-}d_4)$: δ 7.6-7.7 (1H, d); 7.3-7.4 (1H, d); 7.18-7.30 (6H, m); 7.0-7.2 (4H, m); 6.6-6.78 (4H, m); 4.71 (2H, s); 4.64 (2H, s); 4.2-4.3 (1H, m); 1.55-2.2 (10H, m). ESI(-)/MS: 571(M-Li); 367, 255.

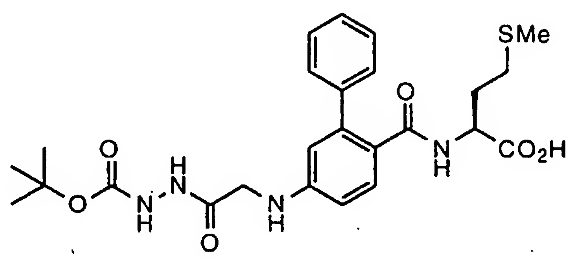


Example782

N-[4-N-(N-phenyl-N-(4-trifluoromethylbenzyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

The desired compound was prepared according to the method of Example 157. ^{1}H(MeOH-d_4): δ 7.55-7.7 (3H, m); 7.3-7.5 (3H, m); 7.2-7.3 (3H, m); 7.0-7.18 (4H, m); 4.8 (4H, d); 4.18-4.3 (1H, m); 1.6-2.2 (10H, m).

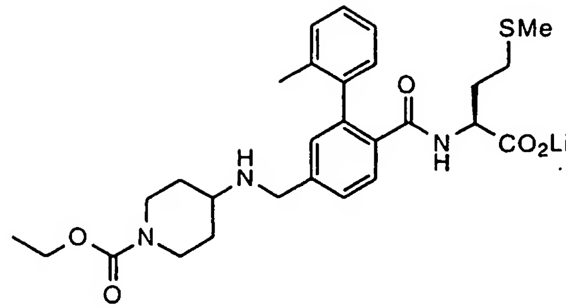
ESI(-)/MS: 605(M-Li); 367; 283.



Example 784

N-[4-N(t-Butylcarbazatocarbonylmethyl)amino-2-phenylbenzoyl]methionine

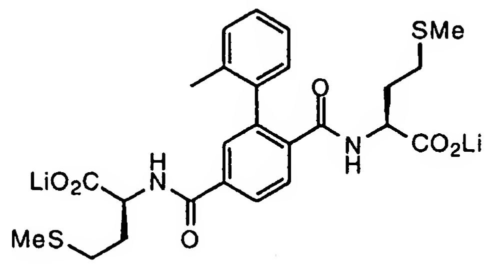
The desired compound was prepared according to the method of Example 57, except t-Butylcarbazatocarbonylmethyl bromide was used as the alkylating agent. ^{1}H nmr (300 MHz, DMSO-d_6): δ 9.79 (s, 1 H), 8.85 (s, 1 H), 8.12 (d, 1 H), 7.47-7.29 (m, 6 H), 6.65 (br d, 1 H), 6.56 (d, 1 H), 6.43 (t, 1 H), 4.30 (m, 1 H), 3.81 (d, 2 H), 2.32 (m, 2 H), 2.05 (br s, 6 H), 1.90 (m, 2 H), 1.47 (s, 9 H). MS (APCI +) m/e 517 $(M+H)^+$.



Example 806

N-[4-(1-ethoxycarbonylpiperidin-4-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

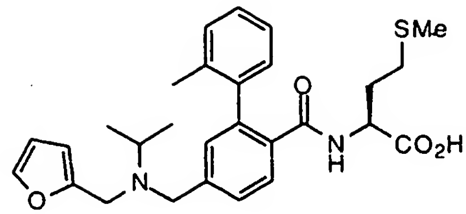
The desired compound was prepared according to the method of Example 158 ^1H nmr (300 MHz, DMSO-d_6): δ 7.48 (d, 1 H), 7.38 (dd, 1 H), 7.26-7.10 (m, 5 H), 6.90 (m, 1 H), 4.00 (q, 2 H), 3.88-3.73 (m, 4 H), 3.66 (m, 1 H), 2.85 (m, 2 H), 2.56 (m, 1 H), 2.18 (m, 2 H), 2.00 (m, 5 H), 1.92 (br s, 3 H), 1. 80 (m, 1 H), 1.76 (m, 1 H). 1.68 (m, 1 H), 1.58 (m, 1 H), 1.16 (t, 3 H). MS (ESI –): m/e 526 $(M-H)^-$.



Example 830

N-[4-(N-[3-methylthio-1-carboxyprop-2-yl]aminocarbonyl)-2-phenylbenzoyl]methionine

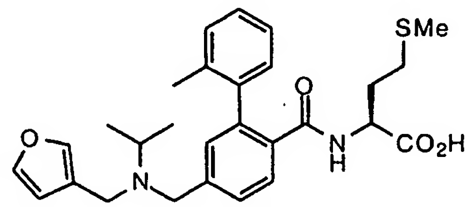
The desired compound was prepared according to the method of Example 451. ^1H NMR (d_6-DMSO): δ 1.64-1.91 (comp, 2 H), 1.93 (s, 3 H), 1.98-2.22 (comp, 10 H), 2.46-2.62 (comp, 2 H), 4.18-4.28 (m, 1 H), 4.49-4.58 (m, 1 H), 7.14-7.26 (comp, 4 H), 7.58 (d, J= 7.8 Hz, 1 H), 7.74-7.79 (br s, 1 H), 7.96 (dd, J= 1.7, 7.8 Hz, 1 H), 8.24-8.32 (br, 1 H), 8.74 (d, J= 7.4 Hz, 1 H), 12.50-12.93 (br, 2 H). LRMS (ESI^-): 517 $(M-1)^-$.



Example 831

N-[4-N-(furan-2-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

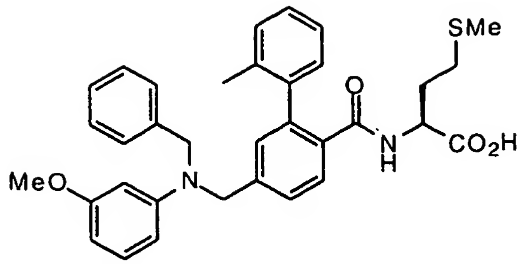
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (d_6-DMSO): δ 1.00 (d, J= 6.6 Hz, 6 H), 1.50-1.63 (m, 1 H), 1.63-1.76 (m, 1 H), 1.77-2.18 (comp, 8 H), 2.89 (sept, J= 6.6 Hz, 1 H), 3.56 (s, 2 H), 3.63 (s, 2 H), 3.66-3.80 (br, 1 H), 6.23 (d, J= 2.9 Hz, 1 H), 6.35 (dd, J= 1.8, 3.3 Hz, 1 H), 6.93 (d, J= 6.2 Hz, 1 H), 7.10-7.26 (br comp, 4 H), 7.37 (d, J= 8.1 Hz, 1 H), 7.48 (d, J= 7.7 Hz, 1 H), 7.53 (dd, J= 0.7, 1.8 Hz, 1 H). LRMS (ESI$^-$): 493 $(M-1)^-$.



Example 832

N-[4-N-(furan-3-ylmethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

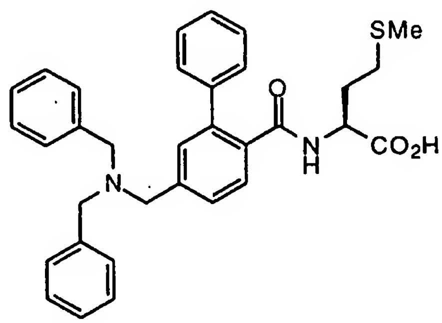
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (d_6-DMSO): δ 1.00 (d, J= 6.6 Hz, 6 H), 1.49-1.76 (comp, 2 H), 1.76-2.19 (comp, 8 H), 2.88 (sept, J= 6.6 Hz, 1 H), 3.37 (s, 2 H), 3.57 (s, 2 H), 3.68-3.78 (br, 21 H), 6.36 (s, 1 H), 6.93 (d, J= 6.2 Hz, 1 H), 7.08-7.26 (comp, 4 H), 7.39 (d, J= 8.1 Hz, 1 H), 7.48 (d, J= 7.6 Hz, 1 H), 7.52-7.57 (comp, 2 H). LRMS (ESI$^-$): 493 $(M-1)^-$.



Example 833

N-[4-N-benzyl-N-3-methoxyphenylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

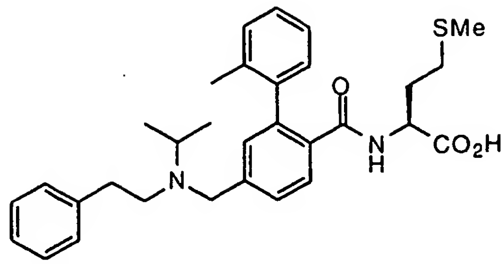
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-2.10 (comp, 10 H), 3.60 (s, 3 H), 3.64-3.74 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.15-6.18 (br comp, 2 H), 6.20 (d, J= 1.9 Hz, 1 H), 6.29 (dd, J= 2.3, 9.2 Hz, 1 H), 6.90-7.03 (comp, 3 H), 7.08-7.34 (comp, 9 H), 7.50 (d, J= 7.7 Hz, 1 H). LRMS (ESI$^-$): 467 $(M-1)^-$.



Example 834

N-[4-N,N-dibenzylaminomethyl-2-phenylbenzoyl]methionine lithium salt

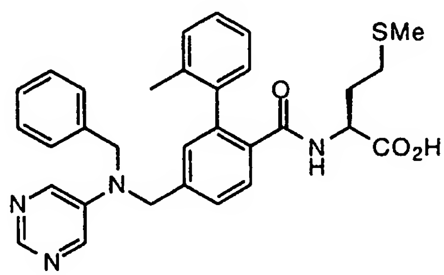
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (d_6-DMSO): δ 1.74-1.95 (comp, 2 H), 1.99 (s, 3 H), 2.15-2.34 (comp, 2 H), 4.17-4.37 (comp, 6 H), 7.21-7.55 (comp, 14 H), 7.60-7.75 (comp, 4 H), 8.57 (d, J= 7.8 Hz, 1 H). LRMS (CI$^+$): 539 $(M+1)^+$.



Example 835

N-[4-N-(2-phenylethyl)-N-isopropylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

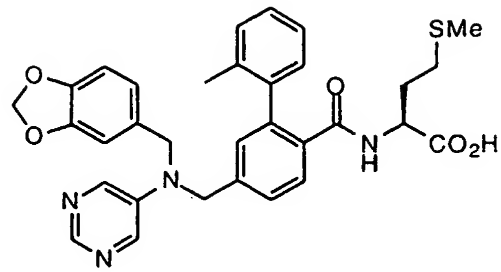
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (d_6-DMSO): δ 0.94 (d, *J*= 6.3 Hz, 6 H), 1.50-1.77 (comp, 2 H), 1.77-2.20 (comp, 8 H), 2.56-2.66 (comp, 4 H), 2.92 (sept, *J*= 6.3 Hz, 1 H), 3.66 (s, 2 H), 3.70-3.81 (br, 1 H), 6.94 (d, *J*= 5.9 Hz, 1 H), 7.07-7.26 (comp, 9 H), 7.32 (d, *J*= 7.7 Hz, 1 H), 7.46 (dd, *J*= 1.8, 7.7 Hz, 1 H). LRMS (ESI$^-$): 517 (M-1)$^-$.



Example 836

N-[4-N-benzyl-N-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl)benzoyl]methionine lithium salt

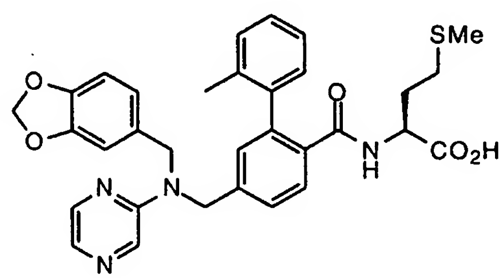
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.86-2.08 (br comp, 8 H), 3.62-3.74 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.92-7.03 (br, 1 H), 7.04-7.38 (comp, 11 H), 7.52 (d, *J*= 8.1 Hz, 1 H), 8.22 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI$^-$): 539 (M-1)$^-$.



Example 837

N-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyrimidin-5-ylaminomethyl-2-(2-methylphenyl) benzoyl]methionine lithium salt

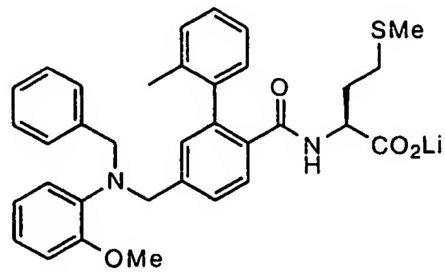
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.46-1.76 (br comp, 2 H), 1.84-2.05 (br comp, 8 H), 3.56-3.67 (br, 1 H), 4.71 (s, 2 H), 4.86 (s, 2 H), 6.77 (dd, *J*= 1.6, 7.8 Hz, 1 H), 6.83-6.88 (comp, 2 H), 6.90-6.98 (br comp, 2 H), 7.0 (s, 1 H), 7.07-7.24 (br comp, 3 H), 7.33 (dd, *J*= 1.9, 8.1 Hz, 1 H), 7.51 (d, *J*= 7.7 Hz, 1 H), 8.23 (s, 2 H), 8.42 (s, 1 H). LRMS (ESI$^-$): 583 (M-1)$^-$.



Example 838

N-[4-*N*-(1,3-benzodiox-5-yl)-*N*-pyridizin-2-ylaminomethyl-2-(2-methylphenyl) benzoyl]methionine lithium salt

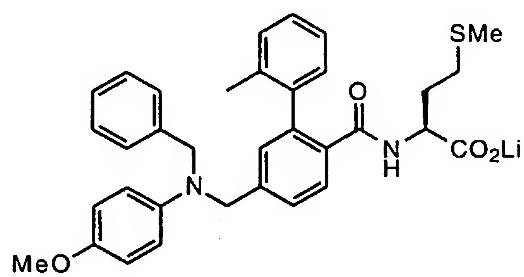
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.49-1.72 (comp, 2 H), 1.88-2.06 (comp, 8 H), 3.60-3.71 (br, 1 H), 4.75-4.80 (br, 2 H), 4.90 (s, 2 H), 5.96 (s, 2 H), 6.75 (dd, *J*= 1.7, 7.8 Hz, 1 H), 6.80-6.83 (comp, 2 H), 6.90-6.96 (comp, 3 H), 7.05-7.22 (br, 3 H), 7.29 (dd, *J*= 1.7, 8.2 Hz, 1 H), 7.49 (d, *J*= 7.8 Hz, 1 H), 7.80 (d, *J*= 2.4 Hz, 1 H), 8.03-8.09 (comp, 2 H).



Example 839

N-[4-(N-benzyl-N-(2-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

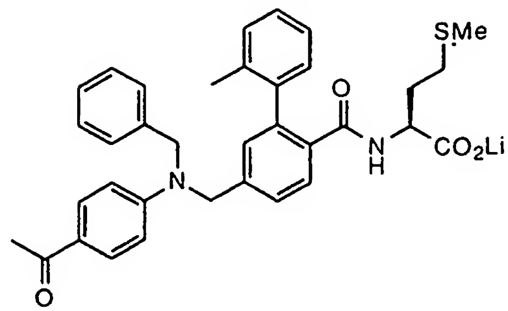
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.47-1.75 (comp, 2 H), 1.76-2.05 (comp, 8 H), 3.66-3.77 (br, 1 H), 3.83 (s, 3 H), 4.22 (s, 2 H), 4.26 (s, 2 H), 6.68-6.74 (m, 1 H), 6.81-6.98 (comp, 4 H), 7.02-7.08 (br, 1 H), 7.10-7.37 (comp, 9 H), 7.44 (d, *J*= 7.8 Hz, 1 H).



Example 840

N-[4-(N-benzyl-N-(4-methoxyphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

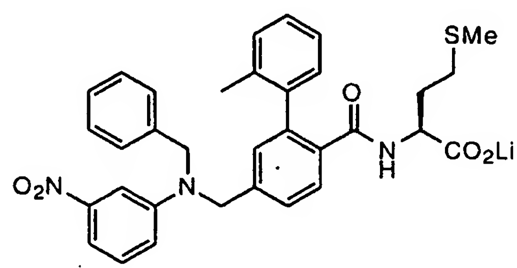
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.49-1.62 (m, 1 H), 1.62-1.75 (m, 1 H), 1.78-2.08 (comp, 8 H), 3.61 (s, 3 H), 3.64-3.76 (br, 1 H), 4.58 (s, 2 H), 4.64 (s, 2 H), 6.62-6.74 (comp, 4 H), 6.89-6.96 (m, 1 H), 7.01 (s, 1 H), 7.08-7.33 (comp, 9 H), 7.47 (d, *J*= 7.8 Hz, 1 H).



Example 841

N-[4-(N-benzyl-N-(4-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

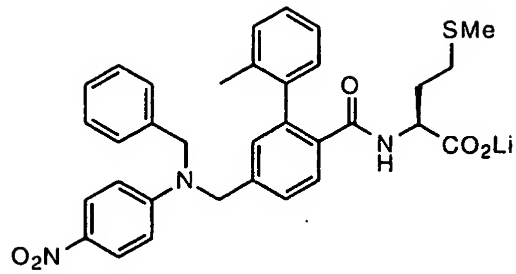
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-1.63 (m, 1 H), 1.63-1.75 (m, 1 H), 1.78-2.10 (comp, 8 H), 2.38 (s, 3 H), 3.66-3.76 (br, 1 H), 4.82 (s, 2 H), 4.88 (s, 2 H), 6.74 (d, *J*= 8.8 Hz, 2 H), 6.95 (d, *J*= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.36 (comp, 9 H), 7.52 (d, *J*= 8.1 Hz, 1 H), 7.72 (d, *J*= 8.8 Hz, 2 H).



Example 842

N-[4-(N-benzyl-N-(3-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

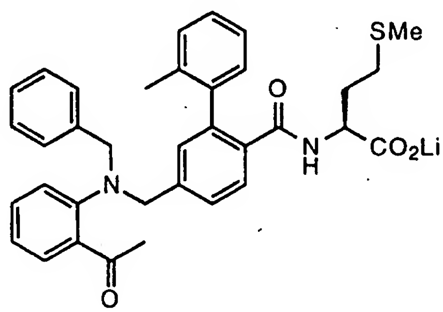
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.49-1.76 (comp, 2 H), 1.77-2.08 (comp, 8 H), 3.67-3.76 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.92-7.01 (br, 1 H), 7.05-7.43 (comp, 14 H), 7.53 (d, *J*= 7.8 Hz, 1 H).



Example 843

N-[4-(N-benzyl-N-(4-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

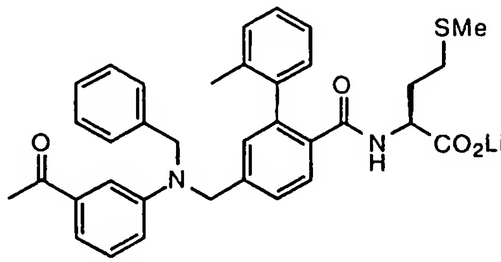
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.48-1.62 (m, 1 H), 1.62-1.74 (m, 1 H), 1.76-2.10 (comp, 8 H), 3.64-3.73 (br, 1 H), 4.90 (s, 2 H), 4.95 (s, 2 H), 6.82 (d, *J*= 9.5 Hz, 2 H), 6.94 (d, *J*= 6.1 Hz, 1 H), 7.02 (s, 1 H), 7.08-7.38 (comp, 9 H), 7.53 (d, *J*= 7.8 Hz, 1 H), 8.00 (d, *J*= 9.5 Hz, 2 H).



Example 844

N-[4-N-(N-benzyl-N-(2-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

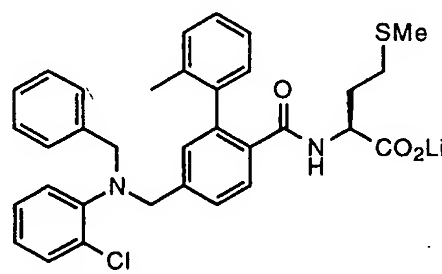
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.45-1.70 (br comp, 2 H), 1.86-2.04 (comp, 8 H), 2.60 (s, 3 H), 3.56-3.66 (br, 1 H), 4.21 (app s, 4 H), 6.82-6.94 (br comp, 2 H), 6.99 (t, *J*= 7.4 Hz, 1 H), 7.08 (d, *J*= 7.7 Hz, 1 H), 7.16-7.34 (comp, 10 H), 7.39 (dd, *J*= 1.9, 7.7 Hz, 1 H), 7.45 (d, *J*= 8.0 Hz, 1 H).



Example 845

N-[4-N-(N-benzyl-N-(3-acetylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

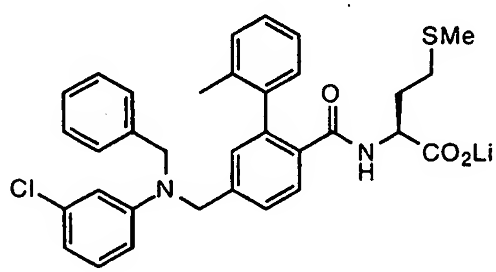
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-1.74 (br comp, 2 H), 1.85-2.08 (comp, 8 H), 2.43 (s, 3 H), 3.62-3.74 (br, 1 H), 4.78 (s, 2 H), 4.84 (s, 2 H), 6.90-7.04 (comp, 2 H), 7.07-7.36 (comp, 13 H), 7.51 (d, J= 7.8 Hz, 1 H)



Example 846

N-[4-N-(N-benzyl-N-(2-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

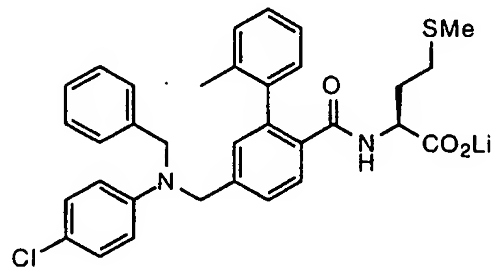
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): ^{1}H NMR (d_6-DMSO): δ 1.46-1.64 (br comp, 2 H), 1.76-2.03 (comp, 8 H), 3.15-3.19 (br, 1 H), 4.23 (s, 2 H), 4.26 (s, 2 H), 6.84-7.47 (comp, 16 H).



Example 847

N-[4-*N*-(*N*-benzyl-*N*-(3-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

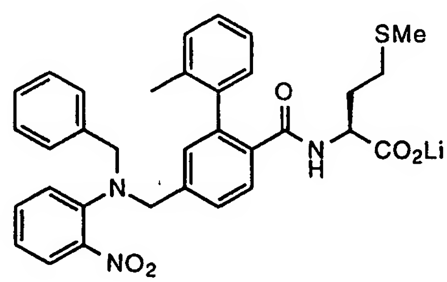
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.88-2.10 (comp, 8 H), 3.64-3.75 (br, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.57-6.66 (comp, 3 H), 6.90-7.36 (comp, 12 H), 7.52 (d, *J*= 7.7 Hz, 1 H).



Example 848

N-[4-*N*-(*N*-benzyl-*N*-(4-chlorophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

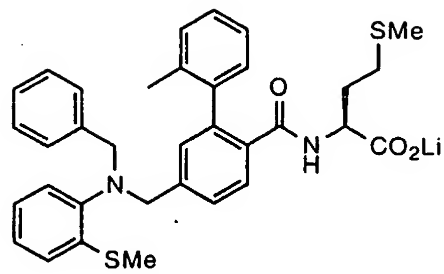
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.47-1.76 (br comp, 2 H), 1.89-2.10 (comp, 8 H), 3.65-3.77 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.62-6.89 (comp, 2 H), 6.90-7.34 (comp, 13 H), 7.51 (d, *J*= 7.8 Hz, 1 H).



Example 849

N-[4-(*N*-benzyl-*N*-(2-nitrophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

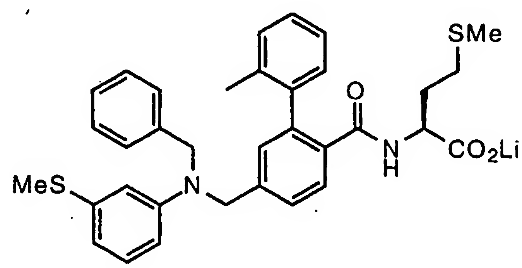
The desired compound was prepared according to the method of Example 157. ^1H NMR (d_6-DMSO): δ 1.46-1.71 (br comp, 2 H), 1.86-2.20 (br comp, 8 H), 3.58-3.70 (br, 1 H), 4.25 (s, 2 H), 4.27 (s, 2 H), 6.85-6.95 (br, 1 H), 6.98-7.36 (comp, 12 H), 7.45 (d, J = 7.8 Hz, 2 H), 7.75 (dd, J = 1.7, 8.2 Hz, 1 H).



Example 850

N-[4-(N-benzyl-N-(2-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

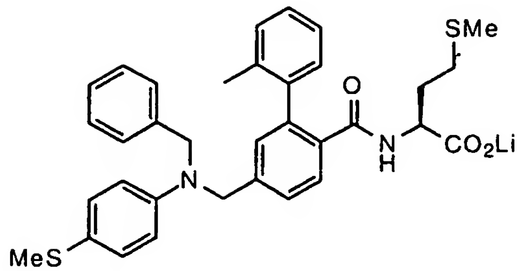
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.86-2.03 (br comp, 8 H), 2.40 (s, 3 H), 3.58-3.68 (br, 1 H), 4.09 (s, 2 H), 4.13 (s, 2 H), 6.83-6.91 (br, 1 H), 6.95-7.31 (comp, 11 H), 7.33-7.44 (comp, 4 H).



Example 851

N-[4-(N-benzyl-N-(3-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

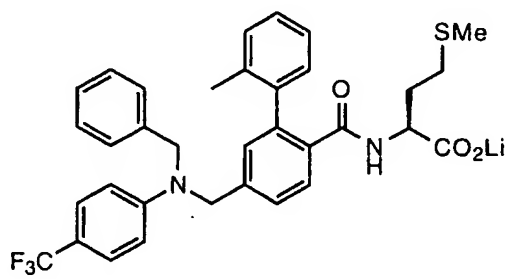
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): ^{1}H NMR (d_6-DMSO): δ 1.48-1.72 (br comp, 2 H), 1.89-2.09 (br comp, 8 H), 2.27 (s, 3 H), 3.62-3.71 (br, 1 H), 4.71 (s, 2 H), 4.77 (s, 2 H), 6.45-6.49 (comp, 3 H), 6.91-7.35 (comp, 12 H), 7.50 (d, J = 8.1 Hz, 1 H).



Example 852

N-[4-(N-benzyl-N-(4-methylthiophenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

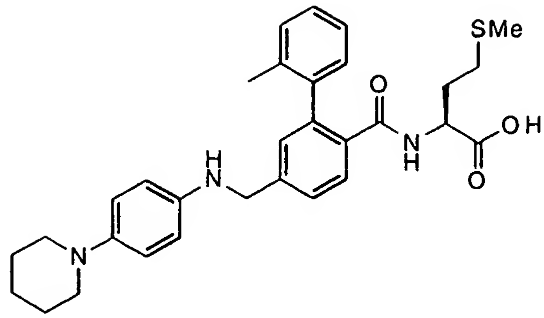
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.45-1.74 (br comp, 2 H), 1.88-2.08 (br comp, 8 H), 2.33 (s, 3 H), 3.58-3.67 (br, 1 H), 4.70 (s, 2 H), 4.76 (s, 2 H), 6.64 (d, J = 8.8 Hz, 2 H), 6.88-6.94 (br, 1 H), 7.00 (s, 1 H), 7.10 (d, J = 8.8 Hz, 2 H), 7.16-7.34 (comp, 9 H), 7.50 (d, J = 7.8 Hz, 1 H).



Example 853

N-[4-(N-benzyl-N-(4-trifluoromethylphenyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

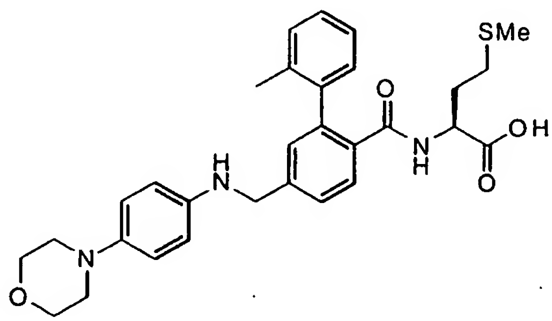
The desired compound was prepared according to the method of Example 157. ^{1}H NMR (d_6-DMSO): δ 1.48-1.75 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 3.64-3.74 (br, 1 H), 4.81 (s, 2 H), 4.86 (s, 2 H), 6.79 (d, J = 8.8 Hz, 2 H), 6.90-7.35 (comp, 11 H), 7.40 (d, J = 8.8 Hz, 2 H), 7.52 (d, J = 7.8 Hz, 1 H).



Example 862

N-[4-N-(4-piperidin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

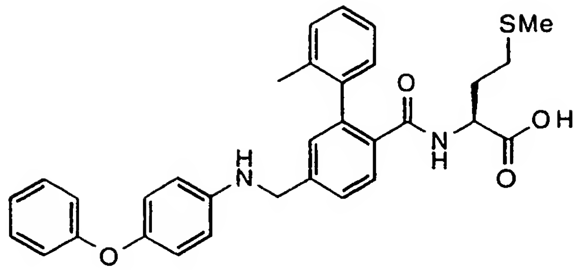
The desired compound was prepared according to the method of Example 158 MS m/e 530 $(M-H)^-$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (m, 3H), 1.78 (m, 4H), 1.85 (m, 1H), 2.0 (m, 8H), 3.03 (m, 4H), 4.3 (m, 3H), 6.13 (m, 1H), 6.54 (m, 2H), 6.98 (m, 2H), 7.10-7.52 (m, 6H), 7.74 (m, 1H).



Example 863

N-[4-N-(4-morpholin-1-ylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

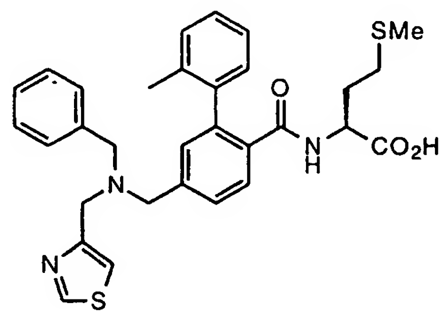
The desired compound was prepared according to the method of Example 158. MS m/e 534 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (m, 1H), 1.83 (m, 1H), 2.0 (m, 8H), 3.00 (m, 4H), 3.85 (m, 4H), 4.35 (m, 3H), 6.03 (m, 1H), 6.58 (m, 2H), 6.80 (m, 2H), 7.22 (m, 6H), 7.85 (m, 1H).



Example 864

N-[4-N-(4-phenoxyphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

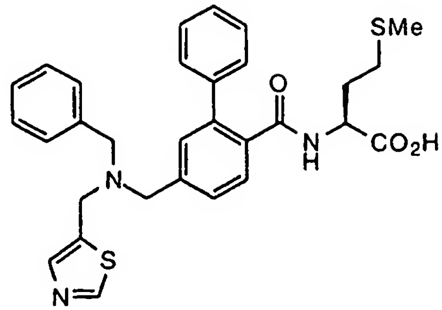
The desired compound was prepared according to the method of Example 158. MS m/e 539 $(M-H)^-$. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.42 (m, 1H), 1.75 (m, 1H), 2.0 (m, 8H), 4.21 (m, 1H), 4.31 (s, 2H), 6.15 (m, 1H), 6.54 (m, 2H), 6.86 (m, 4H), 6.99 (m, 2H), 7.2 (m, 7H), 7.76 (m, 1H).



Example 875

N-[4-N-(benzyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

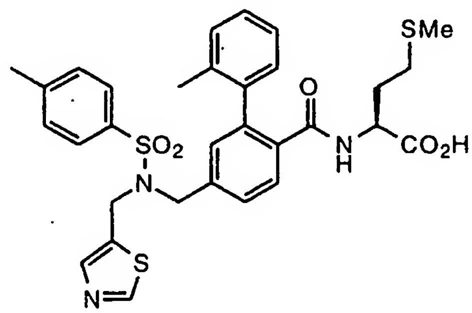
The desired compound was prepared according to the method of Example 158. ^1H (300 MHz, DMSO d_6): δ 9.08, d, 1H; 8.13, d, 1H; 7.58, d, 1H; 7.49, s, 2H; 7.40, d, 2H; 7.31, t, 2H; 7.22, m, 4H; 7.11, m, 2H; 4.21, m, 1H; 3.77, s, 2H; 3.67, s, 2H; 3.62, s, 2H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.63 - 1.90, m, 2H. MS (ESI(-)): 558 (M-H). Calc'd for $C_{31}H_{33}N_3O_3S_2 + 0.49\ H_2O$: C 65.49, H 6.02, N 7.39: Found: C 65.49, H 5.86, N 7.27.



Example 876

N-[4-N-(benzyl-N-thiazol-5-ylmethyl)aminomethyl-2-phenylbenzoyl]methionine

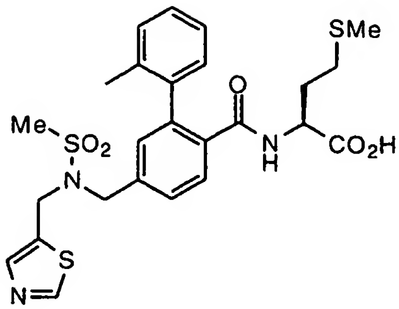
The desired compound was prepared according to the method of Example 158. ^{1}H (300 MHz, DMSO d$_6$): δ 9.04, s, 1H; 8.46, d. 1H; 7.82, s, 1H; 7.3, m, 13H; 4.27, ddd, 1H; 3.83, s, 2H; 3.64, s, 2H; 3.60, s, 2H; 2.21, m, 2H; 1.99, s, 3H; 1.84, m, 2H. MS (ESI(-)): 544 (M-H). Calc'd for $C_{30}H_{31}N_3O_3S_2$: C 66.03, H 5.72, N 7.70: Found: C 65.65, H 5.81, N 7.50.



Example 877

N-[4-N-(toluenesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

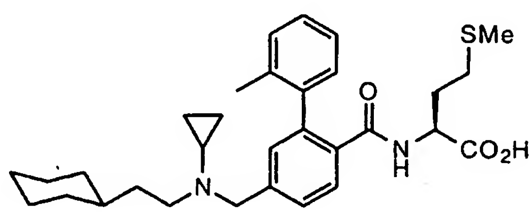
The desired compound was prepared according to the method of Example 157. ^{1}H (300 MHz, DMSO d$_6$): δ 12.62, bs, 1H; 8.94, s, 1H; 8.08, bs, 1H; 7.79, d, 2H; 7.59, s, 1H; 7.41, m, 3H; 7.20, m, 4H; 7.03, bs, 1H; 6.90, bs, 1H; 4.59, s, 2H; 4.38, s, 2H; 4.21, m, 1H; 2.51, s, 3H; 2.40, s, 3H; 2.18, m, 2H; 1.98, s, 3H; 1.78, m, 2H. MS (ESI(-)): 622 (M-H). Calc'd for $C_{31}H_{33}N_3O_5S_3$: C 59.69, H 5.33, N 6.74: Found: C 59.41, H 5.19, N 6.57.



Example 878

N-[4-N-(methanesulfonyl-N-thiazol-2-ylmethyl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

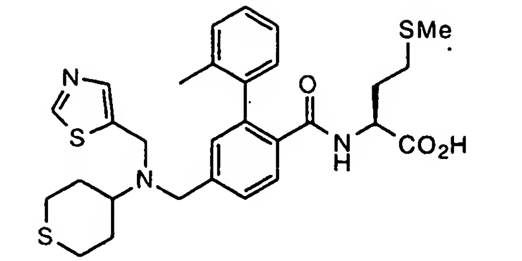
The desired compound was prepared according to the method of Example 157. ^{1}H (300 MHz, DMSO d_6): δ 9.00, s, 1H; 8.11, bs, 1H; 7.52, s, 1H; 7.46, d, 1H; 7.39, dd, 1H; 7.00 - 7.22, m, 5H; 4.63, s, 2H; 4.42, s, 2H; 4.21, m, 1H; 3.02, s, 3H; 1.98 - 2.23, m, 5H; 1.97, s, 3H; 1.64 - 1.91, m, 2H. MS (ESI(-)): 546 (M-H); (ESI(+)): 548. Calc'd for $C_{25}H_{29}N_3O_5S_3$: C 54.82, H 5.34, N 7.67: Found: C 54.60, H 5.32, N .49.



Example 880

N-[4-(*N*-2-Cyclohexylethyl-*N*-cyclopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

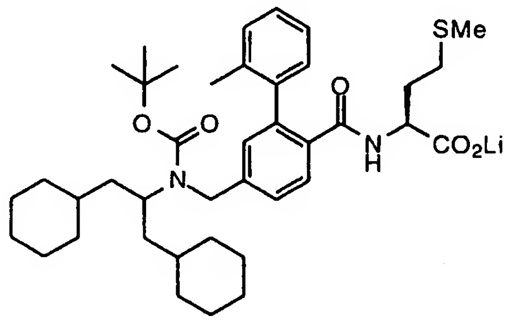
The desired compound was prepared according to the method of Example 158. ^{1}H (300 MHz, DMSO d_6): δ 8.06, d, 1H; 7.47, d, 1H; 7.31, dd, 1H; 7.20, m, 2H; 7.02 - 7.17, m, 3H; 4.21, m, 1H; 3.71, s, 2H; 2.50, m, 2H; 1.98 - 2.23, m, 6H; 1.97, s, 3H; 1.68 - 1.90, m, 3H; 1.50 - 1.66, m, 4H; 1.37, m, 2H; 1.03 - 1.14, m, 4H; 0.81, m, 2H; 0.44, m, 2H; 0.30, m, 2H. MS (ESI(-)): 521 (M-H); ESI((+)): 523 (MH+). Calc'd for $C_{31}H_{42}N_3O_3S$: C 71.23, H 8.10, N 5.36: Found: C 70.25, H 8.05, N 5.31.



Example 881

N-[4-(N-tetrahydrothiopyran-4-yl-N-thiazol-5-ylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

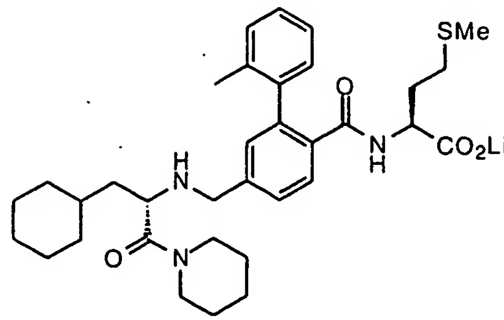
The desired compound was prepared according to the method of Example 158. ^1H (300 MHz, DMSO d_6): δ 8.97, s, 1H; 8.08, d, 1H; 7.78, s, 1H; 7.44, dd, 2H; 7.00 - 7.25, m, 5H; 4.20, ddd, 1H; 3.89, s, 2H; 3.71, s, 2H; 2.38 - 2.70, m, 5H; 1.98 - 2.23, m, 7H; 1.97, s, 3H; 1.59 - 1.91, m, 4H. MS (ESI(-)): 5688 (M-H); ESI((+)): 570. Calc'd for $C_{29}H_{35}N_3O_3S_3 + 0.45\ H_2O$: C 60.27, H 6.26, N 7.27: Found: C 60.27, H 6.32, N 7.17.



Example 886

N-[4-N-t-Butyloxycarbonyl-N-(1,3-dicyclohexylpropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine lithium salt

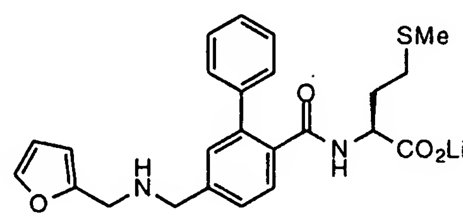
The desired compound was prepared according to the method of Example 158, followed by treatment with di-t-butyl dicarbonate, and hydrolysis. ^1H NMR (300 MHz, DMSO) δ 0.68-0.87 (m, 4H), 0.95-1.10 (m, 13H), 1.28 (s, 3H), 1.40 (s, 6H), 1.50-1.70 (m, 13H), 1.94 (s, 3H), 1.97-2.18 (m, 5H), 3.55-3.70 (m, 1H), 4.20-4.40 (m, 3H), 6.85-6.95 (m, 1H), 7.01-7.27 (m, 5H), 7.30-7.42 (m, 1H), 7.42-7.53 (m, 1H). MS (APCI(+)) *m/z* 679 (M+H); Analysis calc'd for $C_{40}H_{57}LiN_2O_5S \cdot 0.75H2O$: C, 68.79; H, 8.44; N, 4.01; found: C, 68.77; H, 8.33; N, 4.04.



Example 887

N-[4-*N*-(3-Cyclohexyl-1-oxo-1-piperidin-1-ylpropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]-methionine lithium salt

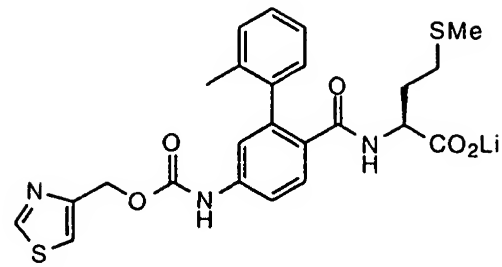
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (300 MHz, DMSO) δ 0.65-0.90 (m, 2H), 1.00-1.24 (m, 10H), 1.30-1.70 (m, 15H), 1.90 (s, 3H), 1.92-2.18 (m, 5H), 3.35-3.80 (m, 3H), 6.85-6.95 (m, 1H), 7.06-7.23 (m, 5H), 7.32 (d, *J*=7.8 Hz, 1H), 7.46 (d, *J*=7.8 Hz, 1H). MS (ESI(-)) *m/z* 592 (M-H); Analysis calc'd for $C_{34}H_{46}LiN_3O_4S \cdot 1.30H2O$: C, 65.53; H, 7.86; N, 6.74; found: C, 65.53; H, 7.36; N, 6.41.



Example 890

N-[4-(N-(furan-2-ylmethyl)aminomethyl)-2-phenylbenzoyl]methionine lithium salt

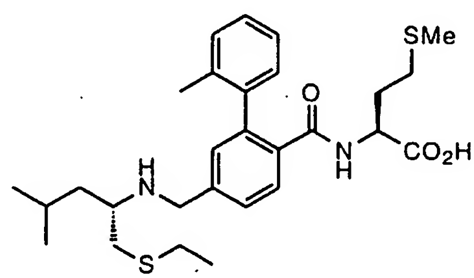
The desired compound was prepared according to the method of Example 158. ^{1}H NMR (DMSO-d_6, 90 °C) δ 7.48-7.24 (m, 9 H), 7.07-7.04 (m, 1 H), 6.37-6.34 (m, 1 H), 6.24-6.20 (m, 1 H), 3.76-3.69 (m, 5 H), 2.43-2.16 (m, 3 H), 2.00-1.66 (m, 5 H); MS *m/z* 439 (M^+ + 1, 100). Anal. Calcd for $C_{24}H_{25}LiN_2O_4S \cdot 2H_2O$ (480.50): C, 59.99; H, 6.08; N, 5.83. Found: C, 59.83; H, 5.83; N, 5.74.



Example 902

N-[4-N-(thiazol-5-ylmethoxycarbonyl)amino-2-(2-methylphenyl)benzoyl]methionine lithium salt

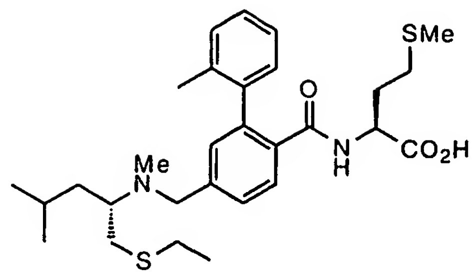
The desired compound was prepared according to the method of Example 57. ^{1}H NMR (DMSO-d_6.) δ 9.93 (s, 1 H), 9.04 (s, 1 H), 7.93 (s, 1 H), 7.44 (s, 2 H), 7.19-7.06 (m, 4 H), 6.92-6.88 (m, 1 H), 6.78-6.74 (m, 1 H), 5.34 (s, 2 H), 3.61-3.56 (m, 1 H), 2.10-1.79 (m, 8 H), 1.77-1.63 (m, 1 H), 1.60-1.53 (m, 1 H); MS *m/z* 498 (M^+ - 1, 100). Exact mass calcd for $C_{24}H_{26}N_3O_5S_2$ 500.1303, found 500.1308.



Example 905

N-[4-(*N*-(1-ethylthio-4-methylpentan-2-yl)aminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

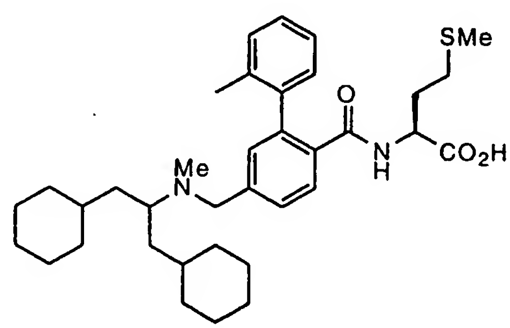
The desired compound was prepared according to the method of Example 158. ^{1}H (300MHz, $CDCl_3$, δ) 7.70 (1H, m), 7.43 (1H, d, *J*=10Hz), 7.30-7.00 (5H, m), 6.25 (1H, m), 4.38 (1H, m), 4.06 (1H, m), 3.91 (1H, bd, *J*=12Hz), 3.01 (1H, m), 2.82 (1H, dd, *J*=15&3Hz), 2.67 (1H, m), 2.45 (2H, q, *J*=8Hz), 2.05 (3H, s), 2.00 (3H, s), 2.00-1.80 (4H, m), 1.67 (1H, m), 1.53 (3H, m), 1.20 (3H, t, *J*=8Hz), 0.92 (3H, d, *J*=8Hz), 0.85 (3H, d, *J*=8Hz). *m/z* (ESI) 517 (MH^+) Anal.calc. for $C_{28}H_{40}N_2O_3S_2$ C 65.08, H 7.80, N 5.42 Found C 65.37, H 7.86, N 5.38



Example 906

N-[4-(N-(1-ethylthio-4-methylpentan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

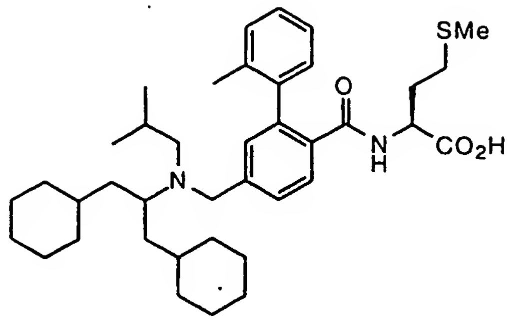
The desired compound was prepared according to the method of Example 158. ^{1}H (300MHz, $CDCl_3$, δ) (rotamer) 7.70 (1H, m), 7.52 (1H, d, J=10Hz), 7.40-7.10 (5H, m), 6.08 (1H, m), 4.43 (1H, m), 3.88 (2H, m), 3.15 (1H, m), 2.87 (1H, dd, J=15&3Hz), 2.60 (1H, m), 2.51 (2H, q, J=8Hz), 2.38 (2.36) (3H, s), 2.06 (2.13) (3H, s), 2.00 (3H, s), 2.00-1.60 (4H, m), 1.60-1.40 (3H, m), 1.22 (3H, t, J=8Hz), 0.92 (3H, d, J=8Hz), 0.88 (3H, d, J=8Hz). m/z (ESI) 531 (MH^+) Anal.calc. for $C_{29}H_{42}N_2O_3S_2 \cdot 0.25\ H_2O$ C 65.07, H 8.00, N 5.23 Found C 65.01, H 7.84, N 5.14



Example 907

N-[4-(N-(1,3-Dicyclohexylpropan-2-yl)-N-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

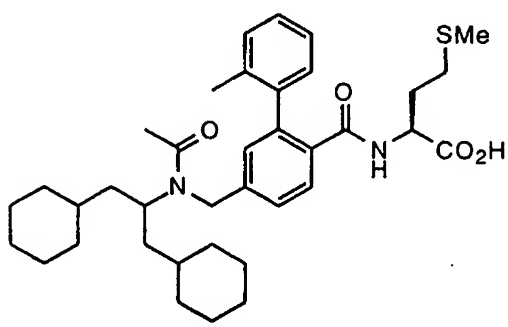
The desired compound was prepared according to the method of Example 158. ^{1}H (300MHz, DMSO-d6, δ) 7.50 (1H, d, J=12Hz), 7.33 (1H, m), 7.25-7.10 (3H, m), 7.08 (1H, m), 6.98 (1H, m), 3.82 (1H, m), 3.55 (2H, m), 2.20-2.00 (3H, m), 2.08 (3H, s), 1.93 (3H, s), 1.82 (3H, s), 1.75-1.40 (12H,m), 1.40-1.20 (5H, m), 1.20-0.90 (9H, m), 0.90-0.70 (3H, m). m/z (ESI) 593 (MH^+)



<u>Example 908</u>

<u>*N*-[4-(*N*-(1,3-Dicyclohexylpropan-2-yl)-*N*-methylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine</u>

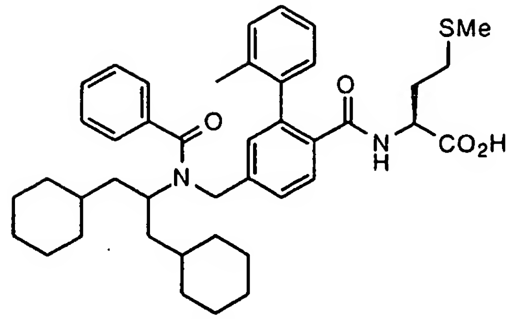
The desired compound was prepared according to the method of Example 158. ^1H (300MHz, DMSO-d6, δ) (rotamer) 7.65 (1H, m), 7.49 (1H, bd, *J*=12Hz), 7.33 (1H, dd, *J*=12&2Hz), 7.30-7.00 (4H, m), 4.50 (2H, m), 4.10 (1H, m), 3.53 (1H, m), 3.20 (1H, m), 2.58 (1H, m), 2.20-2.00 (6H, m), 1.97 (1.92) (3H, s), 1.80-1.40 (14H,m), 1.40-1.20 (4H, m), 1.20-0.90 (8H, m), 0.90-0.60 (9H, d, *J*=9Hz). *m/z* (ESI) 635 (MH^+) Anal.calc. for $C_{39}H_{58}N_2O_3S{\cdot}1.00\ H_2O$ C 71.74, H 9.26, N 4.29 Found C 71.60, H 8.90, N 4.27



<u>Example 909</u>

<u>*N*-[4-(*N*-acetyl-*N*-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine</u>

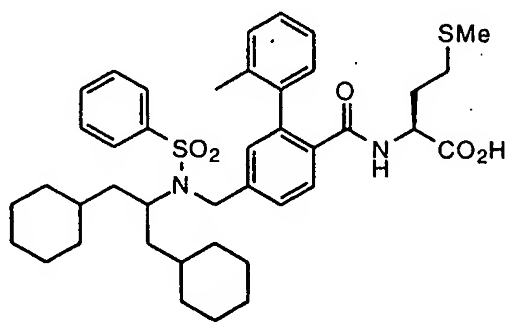
The desired compound was prepared according to the method of Example 158, followed by Schotten-Baumann acylation and subsequent hydrolysis ^1H (300MHz, DMSO-d6, δ) (rotamer) 12.60 (1H, m), 8.05 (1H, m), 7.48 (1H, m), 7.35 (1H, bd, *J*=12Hz), 7.20-6.90 (4H, m), 4.50 (2H, bd, *J*=18Hz), 4.22 (1H, m), 3.87 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 2.08 (3H, s), 1.96 (1.94) (3H, s), 1.80 (3H,m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). *m/z* (ESI) 621 (MH^+) Anal.calc. for $C_{37}H_{52}N_2O_4S{\cdot}0.50\ H_2O$ C 70.55, H 8.48, N 4.45 Found C 70.67, H 8.42, N 4.36\



Example 910

N-[4-(N-benzoyl-N-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 909. ^{1}H (300MHz, DMSO-d6, δ) 12.60 (1H, m), 8.05 (1H, bd, J=12Hz), 7.47 (4H, m), 7.33 (2H, m), 7.25-7.10 (5H, m), 4.62 (2H, bs), 4.21 (1H, m), 3.82 (1H, m), 3.10 (1H, m), 2.20-2.00 (4H, m), 1.96 (3H, s), 1.80 (3H,m), 1.60-1.30 (9H, m), 1.30-1.00 (14H, m), 0.80-0.60 (3H, m). m/z (ESI) 683 (MH^+) Anal.calc. for $C_{42}H_{54}N_2O_4S{\cdot}0.75\ H_2O$ C 72.43, H 8.03, N 4.02 Found C 72.24, H 7.72, N 3.93

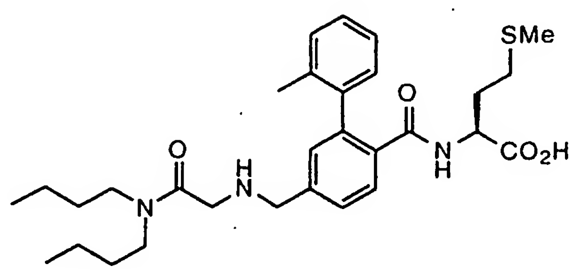


Example 911

N-[4-(N-Benzenesulfoyl-N-(1,3-Dicyclohexylpropan-2-yl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 157. ^{1}H (300MHz, DMSO-d6, δ) 7.83 (2H, bd, J=12Hz), 7.80-7.55 (3H, m), 7.49 (2H, m), 7.30-7.00 (5H, m), 4.43 (2H, m), 4.22 (1H, m), 3.78 (1H, m), 3.20 (1H, m), 2.25-2.00 (4H, m), 1.97 (3H, s), 1.90-1.70 (3H,m), 1.60-1.40 (9H, m), 1.30-0.90 (14H, m), 0.80-0.40

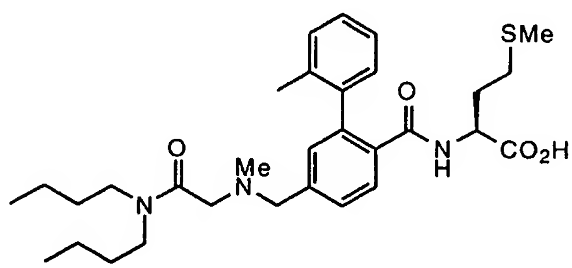
(3H, m). *m/z* (ESI) 719 (MH^+) Anal.calc. for $C_{41}H_{54}N_2O_5S_2 \cdot 0.50\ H_2O$ C 67.64, H 7.61, N 3.85 Found C 67.74, H 7.48, N 3.79



Example 912

N-[4-(*N*-(*N,N*-dibutylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

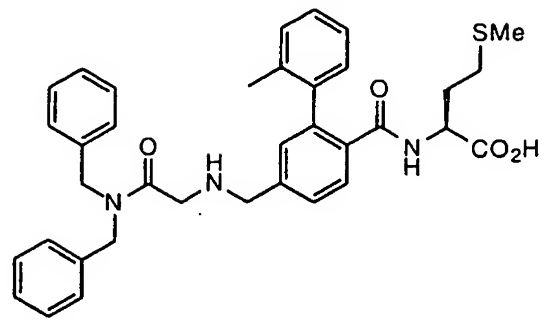
The desired compound was prepared according to the method of Example 158. ^1H (300MHz, DMSO-d6, δ) 7.96 (1H, m), 7.48 (1H, d, *J*=10Hz), 7.39 (1H, dd, *J*=12&2Hz), 7.25-7.00 (4H, m), 4.17 (1H, m), 3.80 (2H, s), 3.23 (2H, t, *J*=8Hz), 3.16 (2H, t, *J*=8Hz), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H,m), 1.41 (4H, m), 1.22 (4H, m), 0.85 (6H, q, *J*=8Hz). *m/z* (DCI, NH_3) 542 (MH^+) Anal.calc. for $C_{30}H_{43}N_3O_4S \cdot 0.75\ H_2O$ C 64.89, H 8.08, N 7.57 Found C 64.83, H 7.94, N 7.33



Example 913

N-[4-(*N*-(*N,N*-dibutylacetamido)-*N*-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

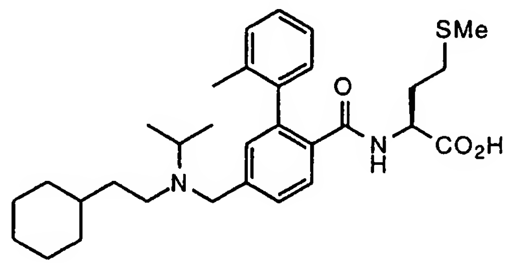
The desired compound was prepared according to the method of Example 158. ^1H (300MHz, DMSO-d6, δ) 7.53 (1H, d, *J*=10Hz), 7.38 (1H, dd, *J*=12&2Hz), 7.25-7.00 (4H, m), 4.23 (1H, m), 3.64 (2H, s), 3.48 (1H, m), 3.35-3.16 (4H, m), 3.14 (1H, m), 2.22 (3H, s), 2.20-2.00 (5H, m), 1.96 (3H, s), 1.90-1.60 (2H,m), 1.42 (4H, m), 1.19 (4H, m), 0.86 (6H, q, *J*=8Hz). *m/z* (ESI) 556 (MH^+) Anal.calc. for $C_{31}H_{45}N_3O_4S$ C 66.99, H 8.16, N 7.56 Found C 66.65, H 8.20, N 7.23



Example 914

N-[4-(N-(N,N-dibenzylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

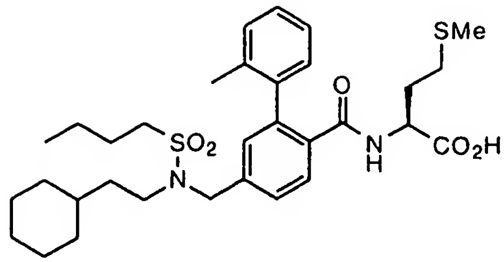
The desired compound was prepared according to the method of Example 158. ^{1}H (300MHz, DMSO-d6, δ) (rotamer) 7.76 (1H, m), 7.40 (1H, d, J=9Hz), 7.30-7.00 (15H, m), 4.41 (4H, d, J=12Hz), 4.10 (1H, m), 3.73 (2H, s), 3.41 (2H, s), 2.20-1.90 (5H, m), 1.87 (1.83) (3H, s), 1.80-1.50 (2H,m). m/z (ESI) 610 (MH$^+$)



Example 915

N-[4-(N-(2-Cyclohexylethyl)-N-isopropylaminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

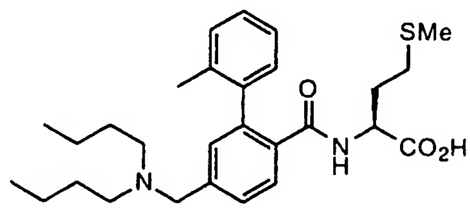
The desired compound was prepared according to the method of Example 158. ^{1}H (300MHz, $CDCl_3$, δ) 7.80-7.60 (2H, m), 7.30-7.00 (5H, m), 6.50 (1H, d, J=8Hz), 4.38 (1H, m), 4.03 (2H, m), 3.67 (1H, m), 2.88 (2H, m), 2.20-2.00 (7H, m), 2.00 (3H, s), 1.80-1.40 (8H, m), 1.33 (6H, d, J=7Hz), 1.30-1.00 (3H, m), 1.00-0.80 (2H, m). m/z (ESI) 525 (MH$^+$) Anal.calc. for $C_{31}H_{44}N_2O_3S{\cdot}0.50\ H_2O$ C 69.76, H 8.50, N 5.25 Found C 69.90, H 8.26, N 5.57



Example 916

N-[4-(N-Butanesulfonyl-N-(2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine

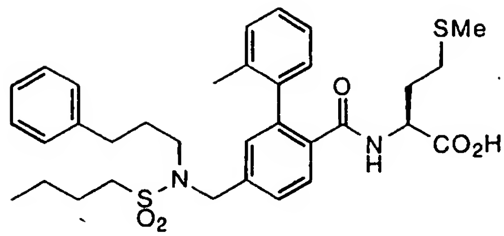
The desired compound was prepared according to the method of Example 157. ^1H (300MHz, $CDCl_3$, δ) 7.99 (1H, m), 7.45 (1H, dd, J=9&2Hz), 7.40-7.10 (5H, m), 5.92 (1H, m), 4.56 (1H, m), 4.44 (2H, s), 3.20 (2H, m), 2.96 (2H, m), 2.20-2.05 (5H, m), 2.02 (3H, s), 2.00-1.70 (3H, m), 1.70-1.30 (10H, m), 1.30-1.00 (4H, m), 0.95 (3H, t, J=8Hz), 0.83 (2H, m). m/z (ESI) 603 (MH^+) Anal.calc. for $C_{32}H_{46}N_2O_5S_2 \cdot 0.25\ H_2O$ C 63.28, H 7.72, N 4.61 Found C 63.27, H 7.73, N 4.50



Example 917

N-[4-(N,N-Dibutylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

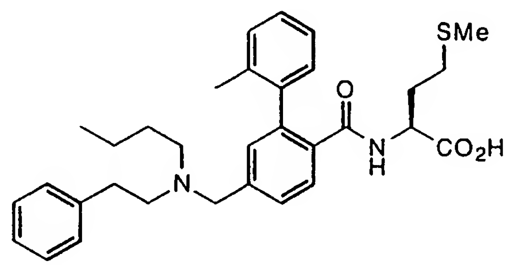
The desired compound was prepared according to the method of Example 158. ^1H (300MHz, $CDCl_3$, δ) 7.75 (1H, d, J=9Hz), 7.67 (1H, m), 7.30-7.10 (5H, m), 6.33 (1H, m), 4.42 (1H, m), 4.13 (2H, m), 2.95 (4H, m), 2.20-2.00 (5H, m), 2.00 (3H, s), 2.00-1.80 (2H,m), 1.68 (4H, m), 1.33 (4H, m), 0.93 (6H, q, J=8Hz). m/z (DCI, NH_3) 485 (MH^+) Anal.calc. for $C_{28}H_{40}N_2O_3S \cdot 1.00\ H_2O$ C 66.90, H 8.42, N 5.57 Found C 66.73, H 8.23, N 5.40



Example 927

N-[4-(N-Butanesulfonyl-N-(3-phenylpropyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

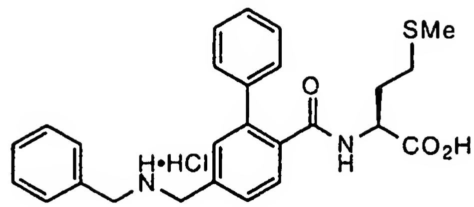
The desired compound was prepared according to the method of Example 157 ^1H (300MHz, $CDCl_3$, δ) 7.97 (1H, m), 7.40 (1H, dd, *J*=9&2Hz), 7.35-7.10 (8H, m), 7.04 (1H, d, *J*=2Hz), 7.03 (1H, s), 5.89 (1H, m), 4.60 (1H, m), 4.43 (2H, s), 3.22 (2H, t, *J*=8Hz), 2.96 (2H, t, *J*=8Hz), 2.55 (2H, t, *J*=8Hz), 2.20-2.05 (2H, m), 2.05 (3H, s), 2.02 (3H, s), 2.00-1.70 (5H, m), 1.57 (1H, m), 1.42 (2H, m), 0.94 (3H, t, *J*=8Hz). *m/z* (ESI) 609 (MH^-) Anal.calc. for $C_{33}H_{42}N_2O_5S_2$ C 64.89, H 6.93, N 4.59 Found C 64.61, H 6.90, N 4.52



Example 928

N-[4-(N-Butyl-N-(2-phenylethyl)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine

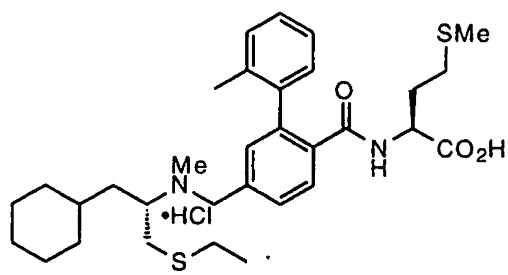
The desired compound was prepared according to the method of Example 157 ^1H (300MHz, $CDCl_3$, δ) 7.78 (1H, d, *J*=9Hz), 7.60 (1H, bd, *J*=8Hz), 7.40-7.20 (5H, m), 7.20-7.00 (5H, m), 6.27 (1H, m), 4.43 (1H, m), 4.20-4.00 (2H, m), 3.20-2.80 (6H, m), 2.20-2.05 (5H, m), 1.98 (3H, s), 1.90 (1H, m), 1.63 (3H, m), 1.32 (2H, m), 0.93 (3H, t, *J*=8Hz). *m/z* (ESI) 533 (MH^+) Anal.calc. for $C_{32}H_{40}N_2O_3S \cdot 1.00\ H_2O$ C 69.79, H 7.69, N 5.09 Found C 70.04, H 7.48, N 4.96



Example 936

N-[4-(N-benzylaminomethyl)-2-phenylbenzoyl]methionine hydrochloride salt

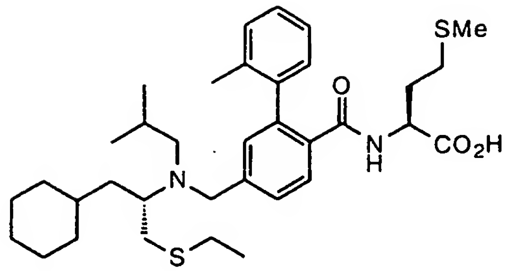
The desired compound was prepared according to the method of Example 158 (DMSO-d6) δ 8.61 (d,1H), 7.61 (m,1H), 7.58 (m, 3H), 7.40 (m, 9H), 4.32 (m, 1H), 4.22 (s, 2H), 4.18 (s, 2H), 2.27 (m, 2H), 2.00 (s, 3H), 1.88 (m, 2H). MS (DCI/NH3) 449 (M+H)+. Anal calcd for $C_{26}H_{29}ClN_2O_3S \cdot 0.80\ H_2O$: C, 62.53; H, 6.18; N, 5.61. Found: C, 62.59; H, 6.31; N, 5.57.



Example 944

N-[4-N-(3-Cyclohexyl-1-ethylthiopropan-2-yl)-N-methylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine hydrochloride salt

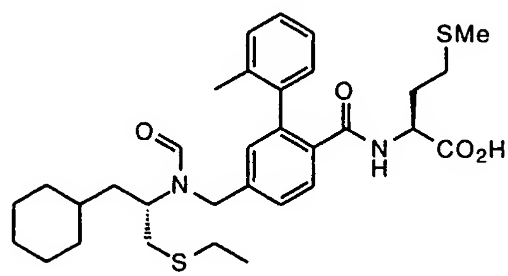
The desired compound was prepared according to the method of Example 158 (DMSO-d6) δ 8.23 (m, 1H), 7.75 (m, 1H), 7.59, 7.50 (both m, total 2H), 7.22, 7.15 (both m, total 4H), 4.50, 4.38 (both m, total 2H), 4.22 (m, 1H), 3.10, 2.90, 2.70 (all m, total 5H), 2.40, 2.10 (both m, total 7H), 1.98 (s, 3H), 1.90-1.40 (envelope, total 10H), 1.15, 1.00, 0.82 (all m, total 7H). MS (ESI) 569 (M-H)-. Anal calcd for $C_{32}H_{47}ClN_2O_3S_2$: C, 63.29; H, 7.80; N, 4.61. Found: C, 63.07; H, 7.79; N, 4.51.



Example 945

N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropan-2-yl)-*N*-isobutylaminomethyl-2-(2-methylphenyl)benzoyl]-methionine

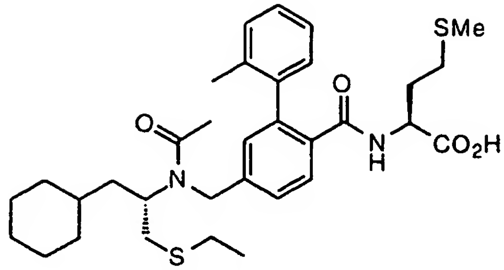
The desired compound was prepared according to the method of Example 158 (DMSO-d_6) δ 8.05 (d, 1H), 7.55 (d, 1H), 7.42 (d, 1H), 7.22, 7.20 (both m, total 5H), 4.27 (m, 1H), 3.73 (d, 1H), 3.60 (d, 1H), 2.90 (dd, 1H), 2.77 (m, 1H), 2.45 (q, 2H), 2.30, 2.10 (both m, total 8H), 2.00 (s, 3H), 1.97-1.25 (envelope, 11H), 1.19 (t, 3H), 1.19-0.70 (envelope, 12H). MS (ESI) 611 $(M-H)^-$. Anal calcd for $C_{33}H_{52}N_2O_3S_2 \cdot 0.25 H_2O$: C, 68.09; H, 8.57; N, 4.54. Found: C, 67.96; H, 8.53; N, 4.49.



Example 946

N-[4-*N*-(3-Cyclohexyl-1-ethylthiopropan-2-yl)-*N*-formylaminomethyl-2-(2-methylphenyl)benzoyl]methionine

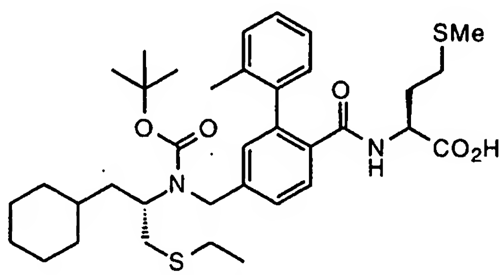
The desired compound was prepared according to the method of Example 607, followed bt Schotten-Baumann acylation. (DMSO-d_6) δ 8.40, 8.27 (both s, total 1H), 8.03, 7.97 (both d, total 1H), 7.45 (m, 2H), 7.20, 7.15 (both m, total 5H), 4.40 (m, 2H), 4.21 (m, 1H), 3.70 (m, 1H), 2.62, 2.46 (both m, total 4H), 2.18, 2.05 (both m, total 5H), 1.96 (s, 3H), 1.90-1.20 (envelope, 9H), 1.10, 1.00, 0.75 (all m, total 9H). MS (ESI) 585 $(M-H)^-$. Anal calcd for $C_{32}H_{44}N_2O_4S_2$: C, 65.72; H, 7.58; N, 4.79. Found: C, 65.47; H, 7.53; N, 4.74.



Example 947

N-[4-N-acetyl-N-(3-Cyclohexyl-1-ethylthiopropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

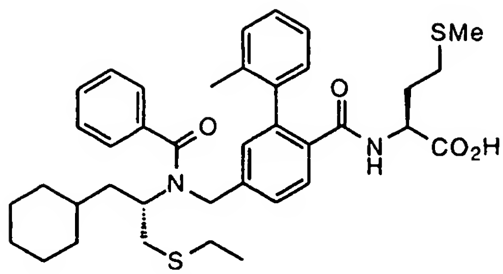
The desired compound was prepared according to the method of Example 946 (DMSO-d_6) δ 8.12, 8.00 (both d, total 1H), 7.55, 7.45, 7.40 (all m, total 2H), 7.20, 7.10, 7.06 (all m, total 5H), 4.65, 4.58 (both m, total 2H), 4.30, 4.20, 3.94 (all m, total 2H), 2.79, 2.60, 2.48 (all m, total 4H), 2.10, 1.97 (m, s, total 11H), 1.90-1.20 (envelope, 9H), 1.15, 1.10, 0.80 (all m, total 9H). MS (ESI) 597 $(M-H)^-$. Anal calcd for $C_{33}H_{46}N_2O_4S_2$: C, 66.19; H, 7.74; N, 4.68. Found: C, 66.02; H, 7.68; N, 4.56.



Example 948

N-[4-N-t-Butyloxycarbonyl-N-(3-cyclohexyl-1-ethylthiopropan-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

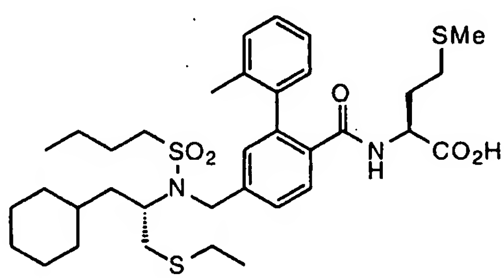
The desired compound was prepared according to the method of Example 946 (DMSO-d_6) δ 7.95 (m, 1H), 7.46 (m, 1H), 7.38 (m, 1H), 7.20, 7.10 (both m, total 5H), 4.40, 4.30, 4.20 (all m, total 4H), 2.60, 2.47 (both m, total 4H), 2.10 (m, 5H), 1.97 (s, 3H), 1.90-1.00 (envelope, 25H), 0.78 (m, 2H). MS (ESI) 655 $(M-H)^-$. Anal calcd for $C_{36}H_{52}N_2O_5S_2$: C, 65.82; H, 7.98; N, 4.26. Found: C, 65.56; H, 7.99; N, 4.20.



Example 949

N-[4-N-Benzoyl-N-(3-Cyclohexyl-1-ethylthiopropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

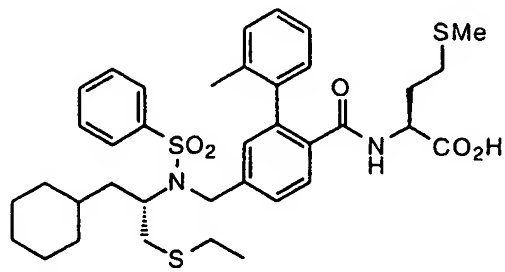
The desired compound was prepared according to the method of Example 946 (DMSO-d_6) δ 8.10 (d, 1H), 7.44 (m, 7H), 7.20 (m, 5H), 4.77, (d, 1H), 4.57 (d, 1H), 4.22 (m, 1H), 3.82 (m, 1H), 2.82 (m, 1H), 2.62 (m, 1H), 2.23, 2.10 (both m, total 7H), 1.97 (s, 3H), 1.80 (m, 2H), 1.48, 1.38 (both m, total 5H), 1.06, 0.65 (both m, total 11H). MS (ESI) 659 $(M-H)^-$. Anal calcd for $C_{38}H_{48}N_2O_4S_2$: C, 69.06; H, 7.32; N, 4.24. Found: C, 68.94; H, 7.31; N, 4.17.



Example 950

N-[4-N-Butanesulfoyl-N-(3-Cyclohexyl-1-ethylthiopropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

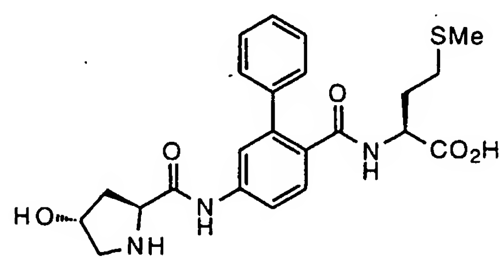
The desired compound was prepared according to the method of Example 157 (DMSO-d_6) δ 8.08 (d, 1H), 7.57 (s, 2H), 7.35, 7.25, 7.18 (all m, total 5H), 4.44 (m, 2H), 4.28 (m, 1H), 3.87 (m, 1H), 3.10 (m, 2H), 2.77, 2.64, 2.55, (all m, total 4H), 2.10 (m, 5H), 2.00 (s, 3H), 1.95-1.50 (envelope, 8H), 1.42, 1.30, 1.20, 1.10 (m, m, t, m, total 12H), 0.90 (t, 3H), 0.80 (m, 2H). MS (ESI) 675 $(M-H)^-$. Anal calcd for $C_{35}H_{52}N_2O_5S_3$: C, 62.10; H, 7.74; N, 4.14. Found: C, 61.86; H, 7.57; N, 4.18.



Example 951

N-[4-N-Benzenesulfonyl-N-(3-cyclohexyl-1-ethylthiopropan-2-yl)aminomethyl-2-(2-methylphenyl)-benzoyl]methionine

The desired compound was prepared according to the method of Example 157 (DMSO-d6) δ 8.07 (d, 1H), 7.86 (d, 2H), 7.70 (m, 1H), 7.64 (m, 2H), 7.50 (s, 2H), 7.20 (m, 5H), 4.50 (m, 2H), 4.22 (m, 1H), 3.72 (m, 1H), 2.50-2.00 (envelope, 10H), 1.98 (s, 3H), 1.80 (m, 2H), 1.42, 1.20, 1.06, 0.90, 0.63 (m, m, t, m, m, total 15H). MS (ESI) 695 $(M-H)^-$. Anal calcd for $C_{37}H_{48}N_2O_5S_3$: C, 63.76; H, 6.94; N, 4.02. Found: C, 63.63; H, 6.93; N, 3.94.



Example 952

N-[4-(4-hydroxyprolinylamino)-2-phenylbenzoyl]methionine

Example 952A

N-[4-N-(N-t-butoxycarbonyl-4-t-butyldimethylsilyloxy-L-prolinyl)amino-2-phenylbenzoyl]-methionine methyl ester

To a solution of N-t-butoxycarbonyl-4-t-butyldimethylsilyloxy-L-proline methyl ester (1.3 g, 3.6 mmol) in methanol (10 mL) was added 1N LiOH (5 mL) in an ice-bath. The reaction mixture was stirred for 30 min. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic solution was washed with 1N HCl and water, dried over anhydrous

magnesium sulfate, and concentrated in vacuo to give the corresponding acid **2** (1.05 g, 96 %) as a foamy solid. Without any purification, **2** (1.0 g, 3.29 mmol) was dissolved in 15 ml of dichloromethane. To this solution was added triethylamine (550 µL, 3.9 mmol) in an ice-bath under argon, followed by IBCF (470 µL, 3.6 mmol). The reaction mixture was allowed to stir for 40 min. At this time TLC showed the absence of the starting material. To this solution 4-amino-2-phenylbenzoyl methionine methyl ester[2] **3** (1.07 g, 2.97 mmol) in dichloromethane (10 mL) was introduced. The reaction mixture was stirred overnight, during which time the ice-bath expired. The reaction mixture was washed with 1N HCl, 5% sodium bicarbonate, and water, dried over magnesiun sulfate, and solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and EtOAc to yield **4** (1.92 g, 94 %) as a foamy solid: mp 83°C; $[\alpha]^{25}_D$ -36.2 (*c*=0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.94 (s, 1H), 7.53-7.26 (m, 8H), 6.41 (d, 1H, *J*=6.0Hz), 4.55 (m, 4H), 3.63 (s, 3H), 3.57 (m, 1H), 3.32 (m, 1H), 2.30 (m, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.83 (m, 1H), 1.73 (m, 1H), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 171.8, 170.7, 169.3, 155.6, 140.0, 129.7, 129.0, 128.5, 128.2, 127.4, 120.2, 117.7, 80.7, 77.2, 70.1, 59.5, 54.7, 52.1, 51.7, 38.0, 30.9, 29.5, 28.2, 25.5, 17.7, 15.1, 4.9; HRMS (EI) calculated for $C_{35}H_{51}N_3O_7SSi$: 685.9498, found: 685.3217. ^1H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (CD_3OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.

Example 952B

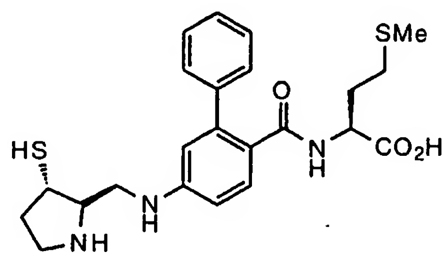
N-[4-*N*-(*N*-*t*-butoxycarbonyl-4-hydroxy-L-prolinyl)amino-2-phenylbenzoyl]methionine methyl ester

To a solution of the above compound (1.82 g, 2.65 mmol) in THF (20 mL) was added 1M TBAF (3 mL). The reaction mixture was stirred for overnight, diluted with EtOAc, and washed 3 times with water. The combined aqueous washings were extracted 3 times with EtOAc. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using ethyl acetate as an eluent to obtain **5** (864 mg, 57%) as a white solid: mp 121-123°C; $[\alpha]^{25}_D$ -53.3 (*c*=0.43, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.60-7.38 (m, 8H), 6.35 (br s, 1H), 4.58-4.51 (br s, 4H), 3.64 (s, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 2.63 (m, 1H), 2.44 (br s, 1H), 2.07 (m, 2H), 1.98 (s, 3H), 1.86 (m, 1H), 1.72 (m, 1H), 1.44 (s, 9H); HRMS (EI) calculated for $C_{29}H_{37}N_3O_7S$: 571.6872, found: 571.2352.

Example 952C

<u>*N*-[4-*N*-(4-hydroxy-L-prolinyl)amino-2-phenylbenzoyl]methionine trifluoroacetate (FTI-2103)</u>

To a solution of the above compound (358 mg, 0.62 mmol) in methanol (6 mL)was added 1N LiOH (1 mL) in an ice bath. The reaction mixture was stirred for 4 hr. The reaction mixture was adjusted to pH=2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with chloroform and water, and extracted 3 times with chloroform. The combined organic solution was washed with 1N HCl and water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the resulting free acid (317 mg, 92 %) as a white solid. To a 5 ml of 1:1 solution of TFA and dichloromethane was added the acid (306 mg, 0.54 mmol). After 3 h, The reaction mixture was thoroughtly evaporated in high vacumm to give an oily residue. The residue was triturate with anhydrous ether and the white solid was collected by filtration to give **6** (254 mg, 72%): HPLC 90% (purity); mp 127 (sub.), 154-157 ^{o}C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.53-7.29 (m, 8H), 4.67 (m, 1H), 4.58 (s, 1H), 4.50 (m, 1H), 2.57 (m, 1H), 2.14 (m, 2H), 2.01 (s, 3H), 1.96 (m, 1H), 1.76 (m, 1H); ^{13}C NMR (CD_3OD) δ 174.8, 172.6, 168.1, 142.4, 141.2, 140.6, 133.2, 130.0, 129.6, 129.5, 128.8, 122.2, 119.3, 71.2, 60.6, 55.2, 52.9, 39.9, 31.4, 30.9, 15.0.



<u>Example 959</u>

<u>*N*-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine</u>

<u>Example 959A</u>

<u>*N*-[4-N-((2R,3R)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester</u>

To a solution of *N*-[4-amino-2-phenylbenzoyl]methionine methyl ester (238 mg, 0.66 mmol) and (2R,3R)-1-*t*-butyloxycarbonyl-3-*t*-butyldimethylsilyloxypyrrolidine-2-carboxaldehyde (158 mg, 0.48 mmol) in methanol (5 mL) was added acetic acid (0.5 mL), followed by sodium cyanoborohydride (65 mg, 1 mmol). The reaction mixture stirred overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5%

sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesiun sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 7:3 solution of hexanes and ethyl acetate to yield the title compound (284 mg, 88 %) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, *J*=8.4 Hz), 7.40 (m, 6H), 6.62 (d, 1H), 6.44 (br s, 1H), 5.65 (d, 1H), 5.43 (s, 1H), 4.61 (m, 1H), 4.41 (br s, 1H), 4.08 (br s, 1H), 3.64 (s, 3H),3.58-3.14 (m, 5H), 2.10 (t, 2H, *J*=7.7 Hz), 2.01 (s, 3H), 1.88 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); 0.88 (s, 9H), 0.07 (s, 6H); HRMS (EI) calculated for $C_{35}H_{53}N_3O_6SSi$: 671.3424, found: 671.3415.

Example 959B

N-[4-N-((2R,3R)-1-*t*-butyloxycarbonyl-3-hydroxypyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 959A (98 mg, 0.14 mmol) in THF (2 mL) was added 1M TBAF-THF (0.18 mL). The reaction mixture was stirred for 15 min at 0^{o}C, diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of ethyl acetate and hexanes to obtain the title compound (60 mg, 76.8 %) as a white solid: mp 67 ^{o}C; $[\alpha]^{25}_D$ +6.32 (*c*=0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, 1H, *J*=8.3 Hz), 7.30 (m, 6H), 6.59 (dd, 1H, *J*=1.2, 8.3 Hz), 6.43 (d, 1H, *J*=2.1 Hz), 5.74 (d, 1H, *J*=7.6 Hz), 5.44 (br s, 1H), 4.57 (m, 1H), 4.40 (m, 1H), 4.07 (br s, 2H), 3.59 (s, 3H), 3.37-3.16 (m, 5H), 2.04(m, 2H), 1.96 (s, 3H), 1.87 (m, 1H), 1.65 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for $C_{29}H_{39}N_3O_6S$: 557.2559, found: 557.2544.

Example 959C

N-[4-N-((2R,3S)-1-*t*-butyloxycarbonyl-3-acetylthiopyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 959B (300 mg, 0.53 mmol) in THF (10 mL) were added TPP (278 mg, 1.06 mmol), followed by DIAD (208 μL, 1.06 mmol) at 0^o C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (76 μL, 1.06 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (211 mg, 64 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, *J*=8.2 Hz), 7.39 (m, 6H), 6.64 (br s, 1H), 6.44 (br s, 1H),

5.66 (d, 1H, *J*=7.4 Hz), 5.39 (br s, 1H), 4.60 (m, 1H), 4.03-3.87 (m, 2H), 3.62 (s, 3H), 3.42-3.11 (m, 5H), 2.33 (s, 3H), 2.07 (t, 2H, *J*=7.6 Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); HRMS (EI) calculated for $C_{31}H_{41}N_3O_6S_2$: 615.2436, found: 615.2437.

Example 959D

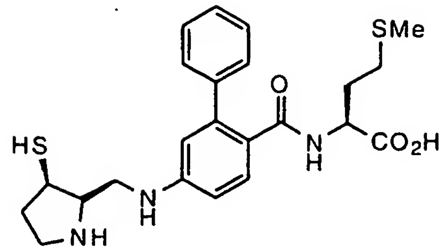
N-[4-N-((2R,3S)-3-acetylthiopyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine hydrobromide

To a solution of the compound prepared in Example 959C (106 mg, 0.17 mmol) in dichloromethane (10 mL) was added 1M boron tribromide-dichloromethane (2.58 mL) at 0° C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue.The residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to give the desired 11 (83 mg, 73.7 %) as a white power: ^{1}H NMR (300 MHz, CD_3OD) δ 7.48-7.35 (m, 6H), 7.01 (d, 1H, *J*= 8.6Hz), 6.64 (s, 1H), 4.45 (dd, 1H, *J*=4.1, 9.2 Hz), 3.92-3.81 (m, 2H), 3.69-3.65 (m, 1H), 3.55-3.40 (m, 4H), 2.55 (m, 1H), 2.32 (s, 3H),2.22 (m, 1H), 2.09 (m, 1H), 2.05 (s, 3H),1.97 (m, 1H), 1.79 (m, 1H).

Example 959E

N-[4-((2S,4S)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine

To a solution of the compound described in Example 959D (80 mg, 0.12 mmol) in TFA (2 mL) was added mercuric acetate (0.38 g, 1.2 mmol) at 0° C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 15 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired 12 (7.7 mg, 10.3 %) as a white powder: ^{1}H NMR (300 MHz, CD_3OD) δ 7.45-7.39 (m, 6H), 6.74 (br s, 1H), 6.70 (br s, 1H), 4.44 (br s, 1H), 3.72-3.30 (m, 7H), 2.56 (br s, 1H), 2.18 (m, 1H), 2.02-1.96 (m, 2H), 2.01 (s, 3H), 1.80 (m, 1H).



Example 960

N-[4-((2S,4R)-4-thiolpyrrolidin-2-ylmethylamino)-2-phenylbenzoyl]methionine

Example 960A

(2R,3S)-1-*Boc*-2-*t*-butyldimethylsilyloxymethyl-3-benzoyloxypyrrolidine

To a solution of (2R,3S)-1-*Boc*-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine (1.52 g, 4.59 mmol) in THF (20 mL) was added TPP (2.41 g, 9.2 mmol), followed by dropwise addition of DIAD (1.82 mL, 9.2 mmol) in THF (10 mL) at 0^{o}C under argon atmosphere. The mixture was allowed for 40 min and benzoic acid (1.12 g, 9.2 mmol) was added dropwisely to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice bath expired. The solvent was removed, and a 3:1 solution of hexanes and ethyl acetate was introduced to the resulting residue to precipitate the insoluble by-products. After removal of by-products, the solution was concentrated. The crude product was chromatographed on silica gel using a 9:1 solution of hexanes and ethyl acetate to yield 14 (1.3 g, 65 %) as a foamy solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.32 (m, 5H), 5.49 (dd, 1H, *J*= 4.2, 11.7 Hz), 3.98-3.52 (m, 5H), 2.40 (m, 1H), 2.07 (m, 1H), 1.47 (s, 9H), 0.89 (s, 9H), 0.05 (s, 6H); MS (EI) *m/z* (relative intensity) 379 ($[M-C_4H_8]^+$, 15), 322 (50), 154 (50), 105 (90), 77 (80).

Example 960B

(2R,3S) 1-*Boc*-2-*t*-butyldimethylsilyloxymethyl-3-hydroxypyrrolidine

To a solution of the compound prepared in Example 960A (1.25 g, 2.86 mmol) in methanol (5 mL) was added 1N LiOH (3 mL) in an ice-bath. The reaction mixture was stirred for 2 hr. The reaction mixture was adjusted to pH2-3 with 1N HCl at the same temperature and the solvent was evaporated. The resulting residue was partitioned with dichloromethane and water, and extracted 3 times with dichloromethane. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 3:1 solution of hexanes and ethyl acetate to obtain the desired compound (275 mg, 30%) as a white solid: mp 118^{o}C; $[\alpha]^{22}_{D}$ -46.7 (*c*=0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (s, 1H), 3.77 (dd, 1H,

J= 3.0, 9.8 Hz), 3.66-3.29 (m, 4H), 2.54 (d, 1H, J= 8.5 Hz), 2.09 (m, 1H), 1.79 (m, 1H), 1.42 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, minor isomer) δ 154.8, 79.7 (79.3), 74.6 (74.1), 67.0 (67.1), 63.2 (62.5), 44.7 (45.2), 31.7 (32.5), 28.7, 26.0, 18.3, -5.2; MS (EI) *m/z* (relative intensity) 275 ([M-C_4H_8]$^+$, 20), 259 (85), 218 (100), 86 (40), 75 (55). 57 (90).

Example 960C

(2R,3S) 1-*Boc*-2-*t*-butyldimethylsilyloxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960B (198 m g, 0.59 mmol) in dry DMF (2 mL) were added tert-butyldimethylsilyl chloride (110 mg, 0.71 mmol) and imidazole (102 mg, 1.5 mmol). The reaction mixture was stirred for 5 hr and then diluted with ether (20 mL).The reaction mixture was washed with brine, 1M HCl, and 5 % sodium bicarbonate. The organic layer was dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (235 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (m, 1H), 3.62-3.20 (m, 5H), 1.88 (m, 1H), 1.62 (m, 1H), 1.36 (s, 9H), 0.78 (s, 18H), -0.03 (s, 12H); MS (CI, isobutane) *m/z* (relative intensity) 446 ([M+H]$^+$, 60), 390 (10), 346 (100).

Example 960D

(2R,3S) 1-*Boc*-2-hydroxymethyl-3-*t*-butyldimethylsilyloxypyrrolidine

To a solution of the compound prepared in Example 960C (229 m g, 0.51 mmol) in THF (2 mL) at 0^{o}C were added water (2 mL) and acetic acid (6 mL). The reaction mixture was stirred for overnight at room temperature. After this time, the reaction mixture was concentrated under reduced pressure. The exess water was removed by azeotroping with toluene. The crude product was purified by flash chromatography on silica gel using a 9:1 solution of hexanes and ethyl acetate to obtain the title compound (96 mg, 56.8%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.41 (br s, 1H), 4.00 (s, 1H), 3.66-3.27 (m, 5H), 1.88 (m, 1H), 1.70 (m, 1H), 1.42 (s, 9H), 0.83 (s, 9H), 0.03 (s, 6H).

Example 960E

N-4-[(2R,3S) 1-Boc-3-*t*-butyldimethylsilyloxypyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine methyl ester

To a solution of DMSO (42 µL, 0.58 mmol) in dichloromethane (2 mL) were added trifluoroacetic anhydride (62 µl, 0.43 mmol) via syringe at -78 ^{o}C under the slight stream of argon. After 10 min, the compound prepared in Example 960D (96 mg, 0.29 mmol) in dichloromethane (2 mL) was added to this mixture at the same temperature. The reaction

mixture was stirred for 1 hr. To this solution was added triethylamine (122 µl, 0.87 mmol). The reaction mixture was allowed for 1 hr at -78°C, slowly warmed to room temperature and concentrated. After usual work-up, the crude aldehyde was used for the next step without purification. To a solution of N-[4-amino-2-phenylbenzoyl]methionine methyl ester hydrochloride (172 mg, 0.29 mmol) and the aldehyde in methanol (5 mL) were added acetic acid (0.5 mL), followed by sodium cyanoborohydride (38 mg, 0.58 mmol). The reaction mixture was allowed to react for overnight. After removal of the solvent, the residue was partitioned with ethyl acetate and 5% sodium bicarbonate, and extracted 3 times with ethyl acetate. The combined organic solution was washed with water and brine, dried over magnesiun sulfate, and the solvent was removed. The residue was flash-chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to yield the title compound (142 mg, 73 %) as a oily residue: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, J=8.0 Hz), 7.35 (m, 6H), 6.55 (d, 1H, J= 8.2 Hz), 6.37 (br s, 1H), 5.67 (d, 1H, J=7.6 Hz), 5.55 (s, 1H), 4.56 (m, 1H), 4.21-3.15 (m, 7H), 3.59 (s, 3H), 2.04 (t, 2H, J=7.7 Hz), 1.95 (s, 3H), 1.83 (m, 1H), 1.60 (m, 1H), 1.42 (s, 9H); 0.82 (s, 9H), -0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, minor isomer) δ 172.1, 168.6, 156.6, 155.0, 150.1 (149.6), 147.7 (141.4), 131.4, 128.8 (128.6), 127.7, 122.6 (122.5), 113.5 (113.7), 110.9, 79.9 (80.2), 74.5, 64.9 (64.7), 60.4, 52.3, 51.8, 47.6, 45.2 (44.8), 33.1, 31.6 (31.9), 29.5, 28.4, 25.7, 21.0, 18.0, 15.3, 14.2, −4.6.

Example 960F

N-4-[(2R,3S) 1-Boc-3-hydroxypyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example960E (140 mg, 0.20 mmol) in THF (3 mL) was added 1M TBAF-THF (0.3 mL). The reaction mixture was stirred for 30 min at 0°C and then quenched with saturated ammonium chloride. The reaction mixture was diluted with ethyl acetate, and washed 3 times with water. The combined aqueous washings were extracted 3 times with ethyl acetate. The combined organic fractions were dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using a 1:1 solution of ethyl acetate and hexanes to obtain the desired compound (85 mg, 76 %) as a oily residue: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 1H, J=8.3 Hz), 7.30 (m, 6H), 6.45 (d, 1H, J=8.5 Hz), 6.31 (br s, 1H), 5.75 (br s, 1H), 5.54 (br s, 1H), 4.51 (m, 1H), 4.15-3.82 (m, 3H), 3.56 (s, 3H), 3.59-2.98 (m, 5H), 2.00 (m, 2H), 1.92 (s, 3H), 1.80 (m, 1H), 1.56 (m, 1H), 1.38 (s, 9H).

Example 960G

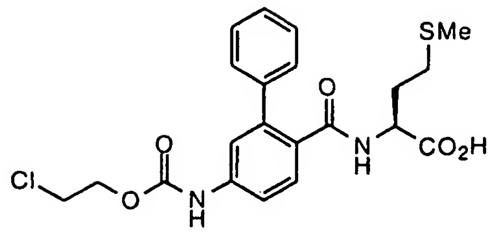
N-4-[(2R,3R) 1-Boc-3-acetylthiopyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine methyl ester

To a solution of the compound prepared in Example 960F (85 mg, 0.15 mmol) in THF (3 mL) were added TPP (80 mg, 0.30 mmol), followed by DIAD (60 μL, 0.30 mmol) at 0^{o} C under argon. The mixture was allowed to stir for 30 min and thiolacetic acid (22 μL, 0.31 mmol) was added to this mixture at the same temperature. The reaction mixture was stirred overnight, during which time the ice-bath expired. The solution was concentrated. The crude products were chromatographed on silica gel using a 1:1 solution of hexanes and ethyl acetate to give the desired compound (80 mg, 86.6 %) as a oily residue: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J*=9.0 Hz), 7.37 (s, 5H), 6.55 (d, 1H, *J*= 7.7 Hz), 6.37 (s, 1H), 5.66 (d, 1H, *J*=7.3 Hz), 5.44 (br s, 1H), 4.58 (m, 1H), 4.40-3.98 (m, 3H), 3.60 (s, 3H), 3.38-3.06 (m, 3H), 2.32 (s, 3H), 2.21 (m, 1H), 2.07 (t, 2H, *J*=7.6 Hz), 1.99 (s, 3H), 1.87 (m, 1H), 1.64 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 194.4, 172.2, 168.5, 156.0, 150.1, 141.8, 141.4, 131.4, 128.8, 128.7, 127.8, 122.2, 113.4, 111.0, 80.5, 60.4, 57.6, 52.4, 51.8, 46.3, 45.1, 44.8, 42.3, 31.7, 30.7, 29.5, 28.4, 15.3, 14.7; HRMS (EI) calculated for $C_{31}H_{41}N_3O_6S_2$: 615.2436, found: 615.2436.

Example 960H

N-4-[(2R,3R) 3-thiopyrrolidin-2-ylmethyl]amino)-2-phenylbenzoyl]methionine hydrobromide

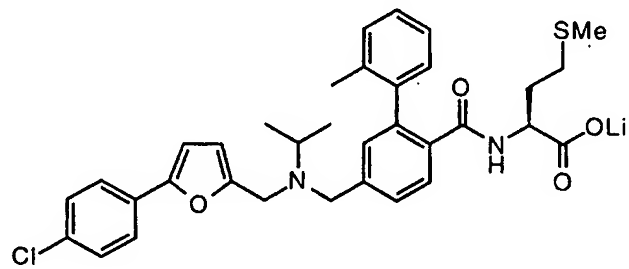
To a solution of the compound prepared in Example 960G (78 mg, 0.12 mmol) in dichloromethane (5 mL) was added 1M boron tribromide-dichloromethane (1.2 mL) at 0^{o} C under argon. The mixture was allowed to stir for 1 hr at the same temperature. Additionally the reaction mixture was stirred 4 hr at room temperature, and quenched by dropwise addition of water (5 mL). The solvent was removed to give crude residue. Without purification, the crude thioacetate was dissolved in TFA (2 mL). To this solution, mercuric acetate (0.1 g, 0.31 mmol) was added at 0^{o} C under argon. The reaction mixture was allowed to stir for 30 min at the same temperature. This solution was evaporated and the resulting solid was suspended in methanol (10 mL). Gaseous hydrogen sulfide was bubbled into the reaction mixture for 5 min. The black precipitate was removed by filtration. After removing methanol, the residue was taken up with a 1:1 solution (1 mL) of water and THF, and purified by Prep-HPLC to afford the desired compound (17 mg, 23 %) as a white powder: ^{1}H NMR (300 MHz, CD_3OD) δ 7.46-7.34 (m, 6H), 6.74 (m, 1H), 6.66 (s, 1H), 4.46 (m, 1H), 4.10-3.91 (m, 2H), 3.75-3.31 (m, 4H), 2.56-2.40 (m, 2H), 2.20-1.78 (m, 4H), 2.01 (s, 3H).



Example 979

N-[4-(N-2-chloroethoxycarbonyl)amino-2-phenylbenzoyl]methionine

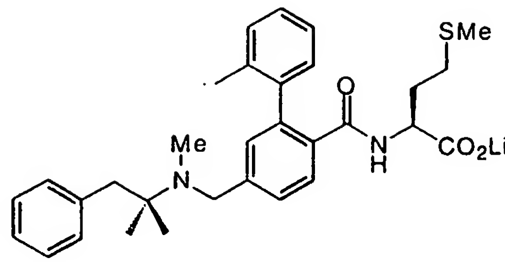
The desired compound was prepared according to the method of Example 57 ^{1}H NMR (CD_3OD): δ 1.68-1.82 (m, 1 H), 1.86-2.03 (comp, 4 H), 2.03-2.26 (comp, 2 H), 3.28 (m, 2 H), 3.72 (t, *J*= 5.8 Hz, 2 H), 4.44 (dd, *J*= 4.4, 9.2 Hz, 1 H), 6.58 (d, *J*= 2.3 Hz, 1 H), 6.66 (dd, *J*= 2.3, 8.5 Hz, 1 H), 7.27-7.46 (comp, 8 H). LRMS (CI): 389 (M-62, loss of COCl)$^+$.



Example 980

N-[4-(*N*-5-(4-Chlorophenyl)furan-2-ylmethyl-N-isopropylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine lithium salt

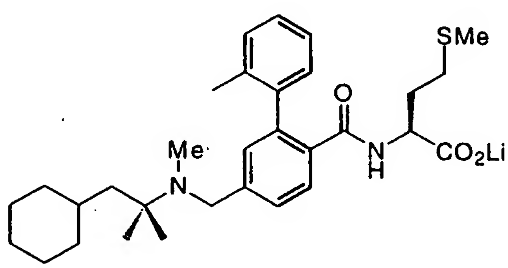
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (300 MHz, d_6 DMSO) δ 7.59 - 7.55 (m, 2H), 7.44 (d, 1H), 7.42 - 7.36 (m, 3H), 7.24 - 7.06 (m, 5H), 6.88 (d, 1H), 6.36 (d, 1H), 3.69 (s, 2H), 3.65 (s, 2H), 2.96 (m, 1H), 2.16 - 1.50 (m, 11H) 1.04 (d, 6H) Calcd for the acid $C_{34}H_{36}O_4N_2SCl$ APCI –Q1MS, MH– 603.



Example 982

N-[4-(N-Methyl-N-(1,1-dimethyl-2-phenylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

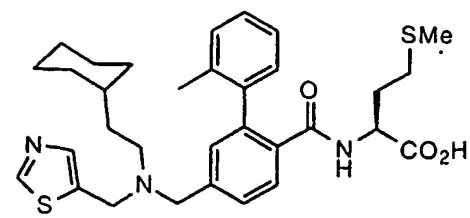
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (300 MHz, DMSO) δ 1.02 (s, 6H), 1.52-1.76 (m, 4H), 1.94 (s, 3H), 1.96-2.04 (m, 3H), 2.17 (s, 3H), 2.78 (s, 2H), 3.64-3.73 (m, 3H), 6.92 (d, J=5.0 Hz, 1H), 7.05-7.23 (m, 10H), 7.34 (dd, J=7.8, 1.5 Hz, 1H), 7.47 (d, J=7.8 Hz, 1H). MS (APCI(+)) *m/z* 518 (M+H); Analysis calc'd for $C_{31}H_{37}LiN_2O_3S$+0.85H_2O: C, 68.96; H, 7.22; N, 5.19; found: C, 68.86; H, 6.60; N, 5.25.



Example 983

N-[4-(N-Methyl-N-(1,1-dimethyl-2-cyclohexylethyl)aminomethyl)-2-(2-methylphenyl)-benzoyl]methionine lithium salt

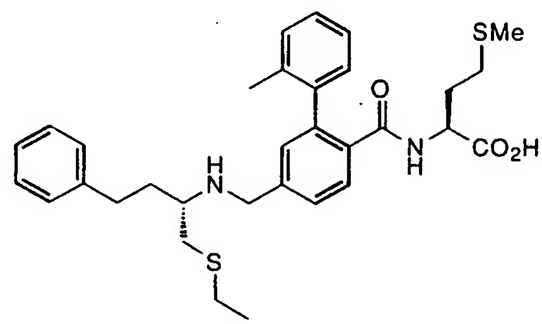
The desired compound was prepared according to the method of Example 158 ^{1}H NMR (300 MHz, DMSO) δ 0.85-1.17 (m, 6H), 1.03 (brs, 6H), 1.30-1.35 (m, 2H), 1.51-1.77 (m, 10H), 1.93 (s, 3H), 1.97-2.18 (m, 3H), 2.02 (s, 3H), 3.56 (brs, 2H), 3.59-3.74 (m, 1H), 6.92 (d, J=5.0 Hz, 1H), 7.11-7.23 (m, 5H), 7.34 (d, J=7.7 Hz, 1H), 7.46 (d, J=7.8 Hz, 1H). MS (APCI(+)) *m/z* 525 (M+H); Analysis calc'd for $C_{31}H_{43}LiN_2O_3S$+0.80H_2O: C, 68.31; H, 8.25; N, 5.14; found: C, 68.29; H, 8.23; N, 5.04.



Example 986

N-[4-(N-2-Cyclohexylethyl-N-thiazol-5-ylmethylaminomethyl)-2-(2-methylphenyl)benzoyl]-methionine

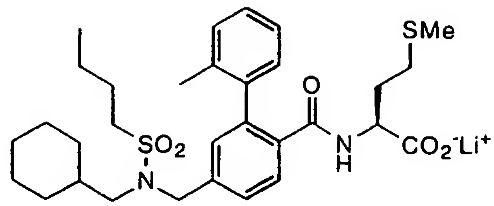
The desired compound was prepared according to the method of Example 157 ^1H nmr (300 MHz, DMSO d_6): δ 9.02, s, 1H; 8.09, d, 1H; 7.76, s, 1H; 7.48, d, 1H; 7.37, dd, 1H; 7.21, m, 2H; 7.15, m, 3H; 4.21, m, 1H; 3.83, s, 2H; 3.61, s, 2H; 2.42, t, 2H; 1.98 - 2.23, m, 6H; 1.96, s, 3H; 1.65- -1.90, m, 2H; 1.55, m, 5H; 1.01 - 1.43, m, 6H; 0.80, m, 2H. MS (ESI(-)): 578 (M-H); (ESI(+)): 580. Calc'd for $C_{32}H_{41}N_3O_3S_2$: C 66.29, H 7.13, N 7.43: Found: C 65.82, H 7.03, N 7.34.



Example 995

N-[4-(1-ethylthio-4-phenylbut-2-oxymethyl)-2-(2-methylphenyl)benzoyl]methionine

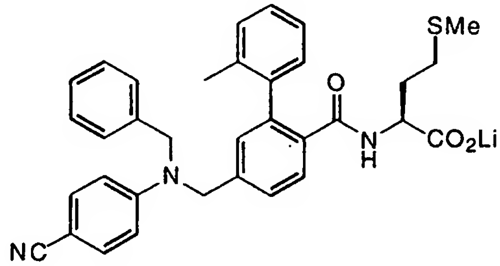
The desired compound was prepared according to the method of Example 158 ^1H (300MHz, $CDCl_3$, δ) 7.70 (1H, m), 7.38 (1H, dd, J=6&2Hz), 7.30-7.20 (6H, m), 7.20-7.05 (3H, m), 7.04 (1H, bs), 6.12 (1H, m), 6.00-5.40 (2H, m), 4.38 (1H, m), 4.01 (1H, m), 3.85 (1H, d, J=12Hz), 3.00-2.50 (5H, m), 2.37 (2H, m), 2.20-2.00 (6H, m), 1.98 (3H, s), 1.86 (2H, m), 1.57 (1H, m), 1.07 (3H, t, J=8Hz). m/e (ESI) 565 (MH^+) Anal.calc. for $C_{32}H_{40}N_2O_3S_2 \cdot 0.50\ H_2O$ C 66.98, H 7.20, N 4.88 Found C 67.02, H 7.24, N 4.80



Example 996

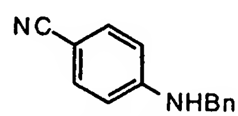
N-[4-(*N*-cyclohexylmethyl-*N*-butanesulfonylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine

The desired compound was prepared according to the method of Example 157 ^1H (300MHz, DMSO-d6, δ) 7.54 (1H, m), 7.42 (1H, m), 7.30-7.10 (5H, m), 6.96 (1H, m), 4.40 (2H, m), 3.63 (1H, m), 3.08 (2H, m), 2.99 (2H, m), 2.17 (2H, m), 1.99 (2H, m), 1.90 (3H, s), 1.80-1.40 (10H, m), 1.37 (4H, m), 1.00 (2H, m), 1.87 (3H, t, J=8Hz), 1.73 (2H, m). m/e (ESI) 587 (MH^-)



Example 997

N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

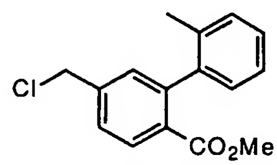


Example 997A

A solution of 4-aminobenzonitrile (2.41 g, 20.0 mmol) and benzaldehyde (2.14 g, 20.0 mmol) in dichloroethane solvent (30 mL) was treated with $Na(OAc)_3BH$ (6.69 g, 30.0 mmol) [CAUTION! - exothermic]. After 16 h the reaction mixture was carefully quenched by the addition of saturated aqueous $NaHCO_3$ (60 mL), and the resulting biphasic mixture was extracted with ethyl acetate (60 mL + 2 x 30 mL). The combined organic extracts were rinsed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to provide an amber oil. Flash column chromatography eluting with hexane and ethyl acetate

using an elution gradient of 90:10 to 80:20 afforded 3.56 g of 997A as a white solid (86% yield).

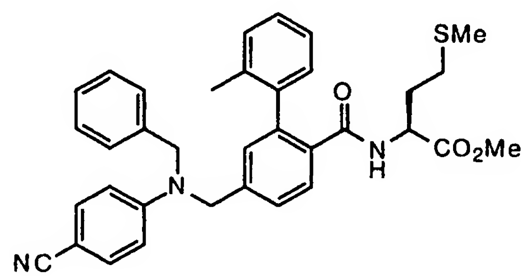
^1H NMR ($CDCl_3$):δ 4.37 (d, J = 5.4 Hz, 2 H), 2.58-4.66 (br, 1 H), 6.58 (d, J = 8.8 Hz, 2 H), 7.26-7.42 (comp, 7 H). LR MS (CI+): $(M+H)^+$ calc for $C_{14}H_{13}N_2$: 209; found: 209.



Example 997B

A solution of 1178C (2.50 g, 9.75 mmol) and lithium chloride (0.537 g, 12.7 mmol) in dimethyl formamide solvent (10 mL) was treated dropwise with a solution of thionyl chloride (1.78 g, 14.6 mmol) in dimethyl formamide solvent (5 mL). After 15 h the reaction mixture was poured into water (125 mL), and the resulting solution was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were rinsed sequentially with water (2 x 20 mL), saturated aqueous sodium bicarbonate (3 x 20 mL), and then brine (20 mL). The organic portion was dried over $MgSO_4$ and concentrated under reduced pressure to provide a colorless oil. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 96:4 to 94:6 afforded 2.63 g of 997B as a colorless oil (98% yield).

^1H NMR ($CDCl_3$):δ 2.06 (s, 3 H), 3.61 (s, 3 H), 4.62 (s, 2 H), 7.07 (d, J = 7.0 Hz, 1 H), 7.17-7.31 (comp, 4 H), 7.45 (dd, J = 1.5, 8.1 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H). LR MS (CI+): $(M+H)^+$ calc for $C_{16}H_{15}ClO_2$: 274; found: 274; $(M+NH_4)+$ calc for $C_{16}H_{18}ClNO_2$: 292; found: 292.

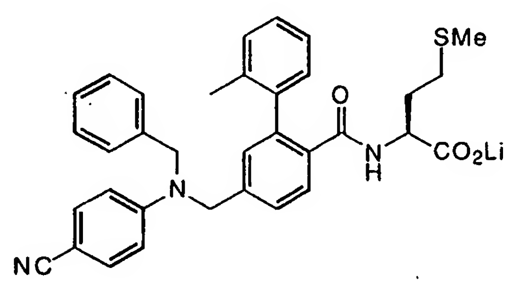


Example 997C

A heterogeneous mixture of 997A (0.466 g, 2.0 mmol), 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B (0.550 g, 2.00 mmol), K_2CO_3 (0.553 g, 4.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent (5 mL) was heated to 70 °C. After 16 h the reaction mixture was returned to room

temperature, diluted with dimethylformamide (DMF) solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 10 h. The reaction mixture was returned to room temperature and diluted with additional DMF (10 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBT) (1.66 g, 10.0 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol). The mixture was heated to 60 °C for 18 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and extracted with 2:1:1 H_2O: saturated aqueous $NaHCO_3$: brine (50 mL + 2 x 20 mL), followed by brine (10 mL). The organic layer was dried over $MgSO_4$, filtered through silica gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 80:20 to 50:50 afforded 0.0365 g of 997C as a colorless oil (3.2% yield).

^{1}H NMR (d_6-DMSO):δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.81-5.90 (br, 1 H), 6.69 (d, J = 8.9 Hz, 2 H), 7.00 (d, J = 1.7 Hz, 1 H), 7.15-7.88 (comp, 10 H), 7.42 (d, J = 8.9 Hz, 2 H), 7.93 (dd, J = 8.1, 13.2 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{35}H_{36}N_3O_3S$: 578; found: 578. LR MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{34}N_3O_3S$: 576; found: 576.

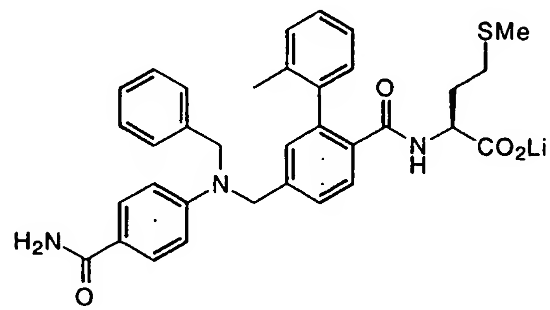


Example 997D

N-[4-N-benzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

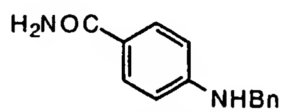
A solution of 997C (0.0375 g, 0.0649 mmol) in methanol solvent (0.3 mL) was treated with LiOH (0.078 mL of a 1 M aqueous solution, 0.078 mmol) to afford a cloudy, white mixture which gradually became clear and colorless. After 8 h the reaction mixture was diluted with H_2O (2 mL) and extracted with diethyl ether (2 x 1 mL). The aqueous phase was lyophilized to provide 0.0332 g of 997D as a white solid (90% yield).

[1]H NMR (d_6-DMSO):δ 1.48-1.76 (comp, 2 H), 1.88-2.08 (comp, 8 H), 3.59-3.72 (br, 1 H), 4.83 (s, 2 H), 4.89 (s, 2 H), 6.76 (d, J = 9.1 Hz, 2 H), 6.90-6.96 (m, 1 H), 7.00 (s, 1 H), 7.07-7.37 (comp, 10 H), 7.47-7.53 (comp, 3 H). HR MS (FAB): $(M+H)^+$ calc for $C_{34}H_{34}N_3O_3S$: 564.2321; found: 564.2325 (0.8 ppm error).



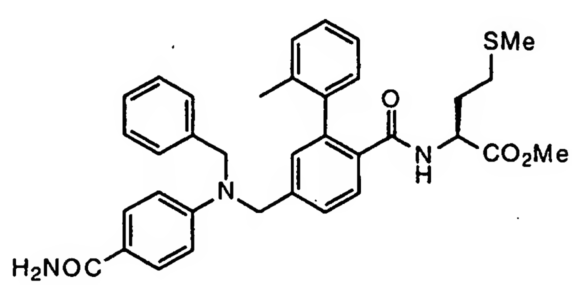
Example 998

N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 998A

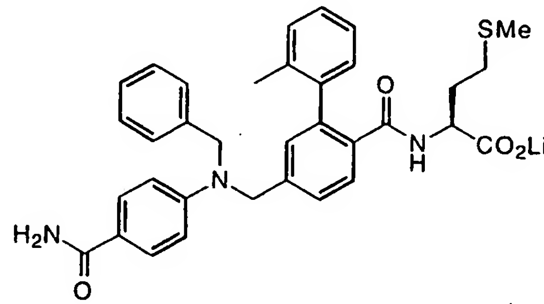
Compound 998A was prepared in the same fashion as 997A (69% yield).
[1]H NMR (d_6-DMSO):δ 4.32 (d, J = 5.9 Hz, 2 H), 6.55 (d, J = 8.6 Hz, 2 H), 6.78-6.92 (br comp, 2 H), 7.20-7.26 (m, 1 H), 7.28-7.38 (comp, 4 H), 7.49-7.59 (br, 1 H), 7.60 (d, J = 8.6 Hz, 2 H). LR MS (CI+): $(M+H)^+$ calc for $C_{14}H_{15}N_2$: 227; found: 227.



Example 998B

Compound 998B was prepared in the same fashion as 997C (5.7% yield).
[1]H NMR (d_6-DMSO):δ 1.70-1.85 (comp, 2 H), 1.96 (s, 3 H), 1.97-2.24 (comp, 5 H), 3.58 (s, 3 H), 4.23-4.33 (br, 1 H), 4.80 (s, 2 H), 4.85 (s, 2 H), 6.68 (d, J = 9.2 Hz, 2

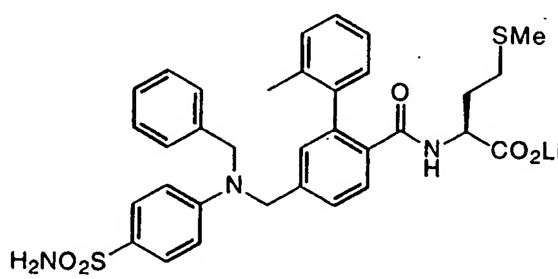
H), 6.86-6.94 (br, 1 H), 7.04-7.36 (comp, 14 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.50-7.60 (br, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 8.30 (d, J = 7.8 Hz, 1 H): LR MS (ESI+): $(M+H)^+$ calc for $C_{35}H_{38}N_3O_4S$: 596; found: 596. LR MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{36}N_3O_4S$: 594; found: 594.



<u>Example 998C</u>

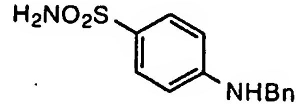
<u>N-[4-N-benzyl-N-(4-carboxamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt</u>

Compound 998C was prepared in the same fashion as 997D (100% yield). ^{1}H NMR (d_6-DMSO):δ 1.47-1.61 (m, 1 H), 1.62-1.73 (m, 1 H), 1.87-2.08 (comp, 8 H), 3.59-3.70 (m, 1 H), 4.78 (s, 2 H), 6.67 (d, J = 8.9 Hz, 2 H), 6.86-6.94 (br comp, 2 H), 7.01 (s, 1 H), 7.05-7.35 (comp, 8 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.54-7.61 (m, 1 H), 7.62 (d, J = 8.9 Hz, 1 H). HR MS (FAB): $(M+Li)^+$ calc for $C_{34}H_{35}LiN_3O_4S$: 588.2508; found: 588.2502 (-1.0 ppm error).



<u>Example 999</u>

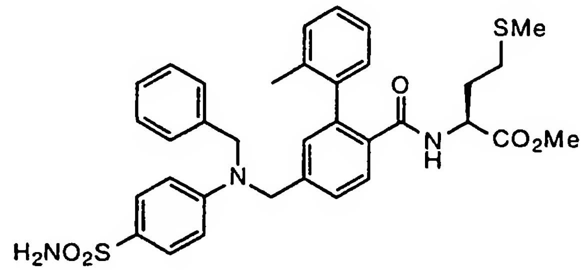
<u>N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt</u>



Example 999A

Compound 999A was prepared in the same fashion as 997A (51% yield). ^{1}H NMR (d_6-DMSO):δ 4.34 (d, J = 6.3 Hz, 2 H), 6.63 (d, J = 8.8 Hz, 2 H), 6.90-6.94 (br, 2 H), 7.00-7.06 (m, 1 H), 7.20-7.26 (m, 1 H), 7.32-7.34 (comp, 4 H), 7.48 (d, J = 8.8 Hz, 2 H). LR

MS (CI+): $(M+H)^+$ calc for $C_{13}H_{15}N_2O_2S$: 263; found: 263.

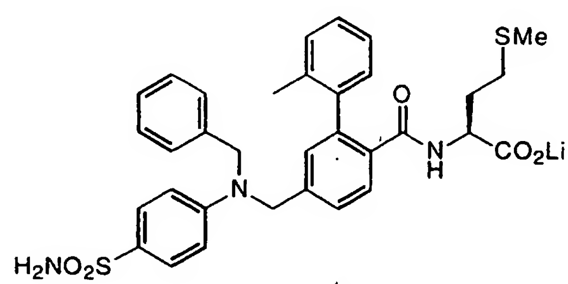


Example 999B

Compound 999B was prepared in the same fashion as 997C (1.3% yield). ^{1}H NMR ($CDCl_3$):δ 1.51-1.63 (m, 1 H), 1.78-1.91 (m, 1 H), 1.95-2.16 (comp, 8 H), 3.63 (app d, J = 4.0 Hz, 3 H), 4.14-4.20 (m, 2 H), 4.37 (d, J = 5.1 Hz, 2 H), 4.52-4.83 (comp, 3 H), 5.83-5.91 (m, 1 H), 6.59 (dd, J = 2.6, 8.8 Hz, 2 H), 7.07 (d, J = 8.1 Hz, 1 H), 7.24-7.40 (comp, 9 H), 7.61 (app t, J = 7.4 Hz, 2 H), 7.85 (dd, J = 7.8, 18.0 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{34}H_{38}N_3O_5S$: 632; found: 632. LR

MS (ESI-): $(M\bullet)^-$ calc for $C_{34}H_{37}N_3O_5S$: 631; found: 631.



Example 999C

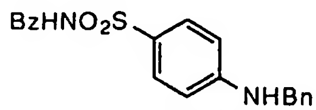
N-[4-N-benzyl-N-(4-sulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 999C was prepared in the same fashion as 997D (90% yield). ^{1}H NMR (d_6-DMSO):δ 1.46-1.82 (comp, 2 H), 1.86-2.16 (comp, 8 H), 3.59-3.73 (m, 1 H), 3.99 (s, 2 H), 4.31 (app d, J = 5.9 Hz, 2 H), 6.55 (d, J = 8.0 Hz, 2 H), 6.74-7.37 (comp, 14 H), 7.72-7.80 (br, 1 H). HR

MS (FTMS): $(M+H)^+$ calc for $C_{33}H_{36}N_3O_3S_2$: 618.2087; found: 618.2091 (-0.7 ppm error).

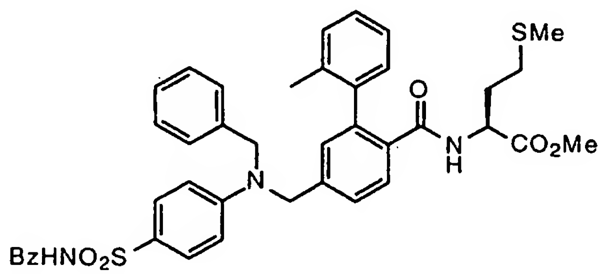
Example 1000

N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



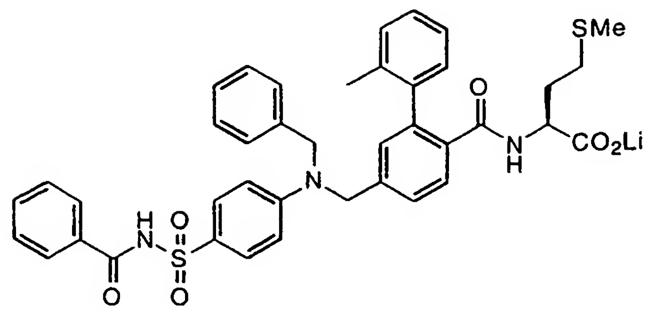
Example 1000A

Compound 1000A was prepared in the same fashion as 997A (81% yield). ^1H NMR ($CDCl_3$):δ 4.39 (d, J = 4.7 Hz, 2 H), 4.67-4.73 (br, 1 H), 6.62-6.67 (m, 2 H), 7.29-7.42 (comp, 5 H), 7.43-7.47 (comp, 2 H), 7.53-7.59 (m, 1 H), 7.74-7.79 (m, 2 H), 7.92-7.95 (m, 2 H), 8.46-8.80 (br, 1 H). LR
MS (CI+): $(M+H)^+$ calc for $C_{20}H_{19}N_2O_2S$: 367; found: 367.



Example 1000B

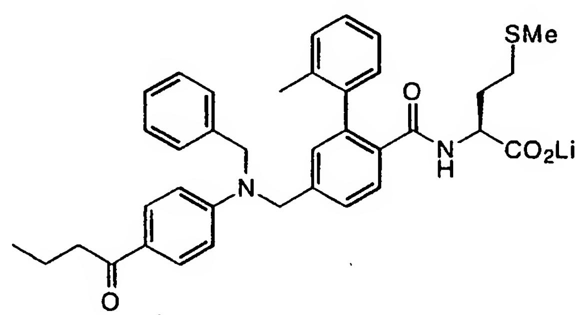
Compound 1000B was prepared in the same fashion as 997C (5.6% yield). ^1H NMR ($CDCl_3$):δ 1.52-1.66 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 8 H), 3.65 (s, 3 H), 4.56-4.66 (m, 1 H), 4.72 (s, 2 H), 4.75 (s, 2 H), 5.86-5.93 (br, 1 H), 6.60-6.78 (comp, 2 H), 7.12-7.37 (comp, 9 H), 7.37-7.45 (comp, 3 H), 7.50-7.57 (m, 1 H), 7.87 (d, J = 7.8 Hz, 2 H), 7.86-7.94 (comp, 5 H), 8.02 (s, 1 H), 9.38 (s, 1 H), 10.70-10.86 (br, 1 H). LR
MS (ESI+): $(M+H)^+$ calc for $C_{41}H_{42}N_3O_6S$: 736; found: 736. LR
MS (ESI-): $(M-H)^-$ calc for $C_{41}H_{40}N_3O_6S$: 734 found: 734.



Example 1000C

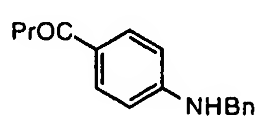
N-[4-N-benzyl-N-(4-N-benzoylsulfonamidophenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1000C was prepared in the same fashion as 997D (77% yield). ^1H NMR (d_6-DMSO):δ 1.48-1.76 (comp, 2 H), 1.89-2.06 (comp, 8 H), 3.67-3.77 (br, 1 H), 4.29 (d, J = 5.9 Hz, 1 H), 4.74 (s, 2 H), 4.79 (s, 2 H), 6.49 (d, J = 8.9 Hz, 1 H), 6.60-6.66 (m, 2 H), 6.95-7.35 (comp, 15 H), 7.47-7.58 (comp, 2 H), 7.86 (d, J = 7.2 Hz, 2 H). LR MS (ESI-): $(M-H)^-$ calc for $C_{40}H_{38}N_3O_6S_2$: 720; found: 720.



Example 1001

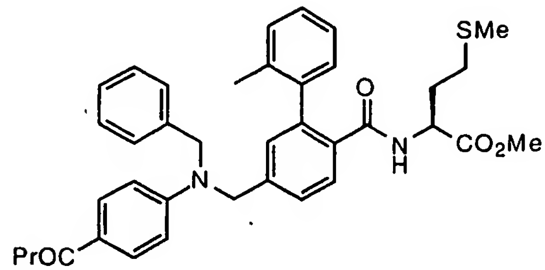
N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1001A

Compound 1001A was prepared in the same fashion as 997A (89% yield). ^1H NMR ($CDCl_3$):δ 0.97 (t, J = 7.4 Hz, 3 H), 1.73 (tq, J = 7.3, 7.4 Hz, 2 H), 2.82 (t, J = 7.3 Hz, 2 H), 4.39 (d, J = 4.0 Hz, 2 H), 4.56-4.63 (br, 1 H), 6.59 (d, J = 9.0 Hz, 2 H), 7.25-7.35 (comp, 5 H), 7.82 (d, J = 9.0 Hz, 2 H). LR

MS (CI+): $(M+H)^+$ calc for $C_{17}H_{20}NO$: 254; found: 254.



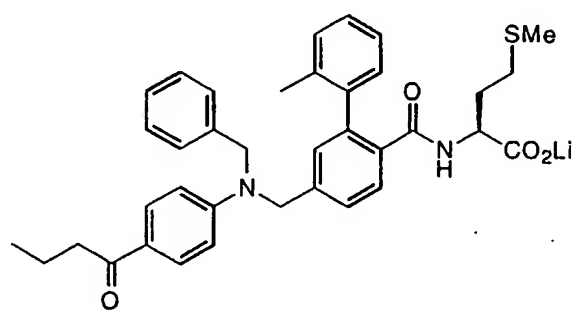
Example 1001B

Compound 1001B was prepared in the same fashion as 997C (49% yield).

^1H NMR ($CDCl_3$):δ 0.97 (t, J = 7.5 Hz, 3 H), 1.52-1.66 (m, 1 H), 1.73 (app q, J = 7.5 Hz, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.13 (comp, 8 H), 2.82 (t, J = 7.5 Hz, 2 H), 3.66 (s, 3 H), 4.53-4.67 (m, 1 H), 4.73 (s, 2 H), 4.76 (s, 2 H), 5.84-5.90 (m, 1 H), 6.71 (d, J = 8.9 Hz, 2 H), 7.04 (d, J = 1.7 Hz, 1 H), 7.14-7.37 (comp, 10 H), 7.82 (d, J = 8.9 Hz, 2 H), 7.92 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{38}H_{43}N_2O_4S$: 623; found: 623. LR

MS (ESI-): $(M-H)^-$ calc for $C_{28}H_{41}N_2O_4S$: 621; found: 621.



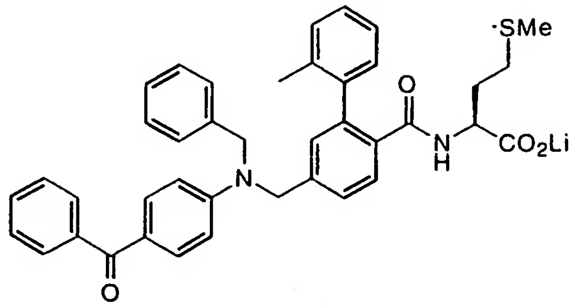
Example 1001C

N-[4-N-benzyl-N-(4-propionylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1001C was prepared in the same fashion as 997D (98% yield).

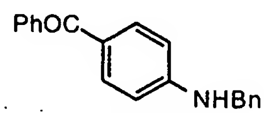
^1H NMR (d_6-DMSO):δ 0.88 (t, J = 7.3 Hz, 3 H), 1.50-1.63 (comp, 3 H), 1.63-1.78 (m, 1 H), 1.79-2.11 (comp, 8 H), 2.78 (t, J = 7.3 Hz, 2 H), 3.72-3.81 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.74 (d, J = 9.2 Hz, 2 H), 6.94-7.02 (br, 1 H), 7.02 (s, 1 H), 7.09-7.36 (comp, 10 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.73 (d, J = 9.2 Hz, 2 H). HR

MS (FAB): $(M+2Li-H)^+$ calc for $C_{37}H_{39}Li_2N_2O_4S$: 621.2951; found: 621.2966 (2.4 ppm error).



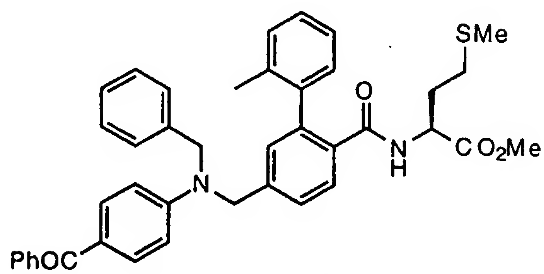
<u>Example 1002</u>

<u>N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt</u>



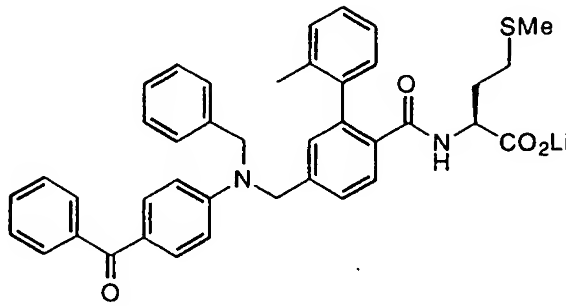
<u>Example 1002A</u>

Compound 1002A was prepared in the same fashion as 997A (63% yield). ^{1}H NMR (d_6-DMSO):δ 3.37 (s, 1 H), 4.38 (d, J = 6.2 Hz, 2 H), 6.68 (d, J = 8.8 Hz, 2 H), 7.22-7.28 (m, 1 H), 7.31-7.38 (comp, 4 H), 7.46-7.62 (comp, 7 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{20}H_{18}NO$: 288; found: 288. LR MS (ESI-): $(M-H)^-$ calc for $C_{20}H_{16}NO$: 286; found: 286.



<u>Example 1002B</u>

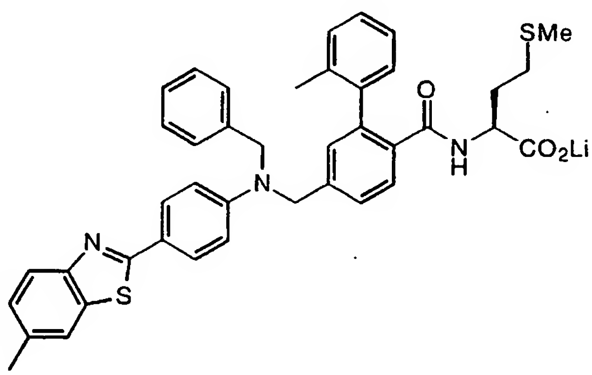
Compound 1002B was prepared in the same fashion as 997C (30% yield). ^{1}H NMR ($CDCl_3$):δ 1.52-1.68 (m, 1 H), 1.79-1.93 (m, 1 H), 1.98-2.16 (comp, 8 H), 3.67 (s, 3 H), 4.56-4.70 (m, 1 H), 4.76 (s, 2 H), 4.78 (s, 2 H), 5.85-5.92 (m, 1 H), 6.74 (d, J = 9.2 Hz, 2 H), 7.05 (s, 1 H), 7.14-7.38 (comp, 10 H), 7.40-7.48 (comp, 2 H), 7.69-7.78 (comp, 4 H), 7.94 (dd, J = 8.1, 13.3 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{41}H_{41}N_2O_4S$: 657; found: 657. LR MS (ESI-): $(M-H)^-$ calc for $C_{41}H_{39}N_2O_4S$: 655; found: 655.



Example 1002C

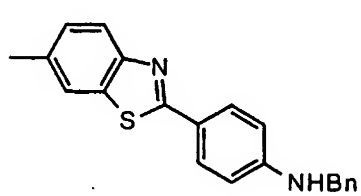
N-[4-N-benzyl-N-(4-benzoylphenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1002C was prepared in the same fashion as 997D (86% yield). ^{1}H NMR (d_6-DMSO):δ 1.49-1.63 (m, 1 H), 1.63-1.77 (m, 1 H), 1.78-2.10 (comp, 8 H), 3.68-3.76 (br, 1 H), 4.84 (s, 2 H), 4.89 (s, 2 H), 6.81 (d, J = 9.1 Hz, 2 H), 6.96 (d, J = 5.4 Hz, 1 H), 7.03 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.46-7.61 (comp, 7 H). HR MS (FAB): $(M+Li)^+$ calc for $C_{40}H_{38}LiN_2O_4S$: 649.2712; found: 649.2723 (1.6 ppm error). .



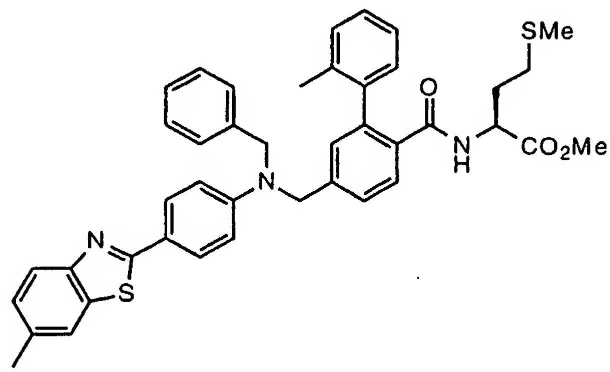
Example 1003

N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2yl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



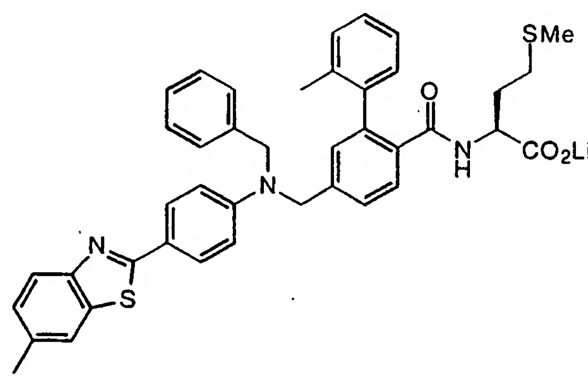
Example 1003A

Compound 1003A was prepared in the same fashion as 997A (38% yield). ^1H NMR ($CDCl_3$):δ 2.47 (s, 3 H), 4.41 (app s, 3 H), 6.65-6.70 (m, 2 H), 7.22-7.38 (comp, 6 H), 7.62 (s, 1 H), 7.83-7.91 (comp, 3 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{21}H_{19}N_2S$: 330; found: 330. LR MS (ESI-): $(M-H)^-$ calc for $C_{21}H_{17}N_2S$: 329; found: 329.



Example 1003B

Compound 1003B was prepared in the same fashion as 997C (16% yield). ^1H NMR ($CDCl_3$):δ 1.52-1.72 (br m, 1 H), 1.80-1.92 (m, 1 H), 1.99-2.14 (comp, 8 H), 2.48 (s, 2 H), 3.66 (s, 3 H), 4.56-4.68 (m, 1 H), 4.74 (s, 2 H), 4.77 (s, 2 H), 5.84-5.90 (m, 1 H), 6.79 (d, J = 8.8 Hz, 2 H), 7.07 (s, 1 H), 7.24-7.38 (comp, 11 H), 7.62 (s, 2 H), 7.85-7.98 (comp, 4 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{42}H_{42}N_3O_3S_2$: 698; found: 698. LR MS (ESI-): $(M-H)^-$ calc for $C_{42}H_{40}N_3O_3S_2$: 700; found: 700.

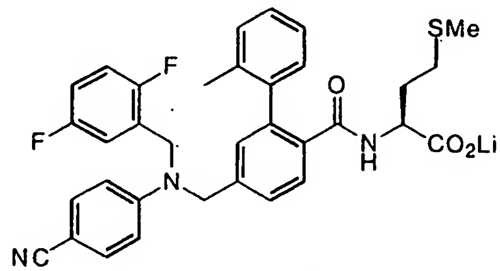


Example 1003C

N-[4-N-benzyl-N-(4-(6-methylbenzthiazol-2yl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

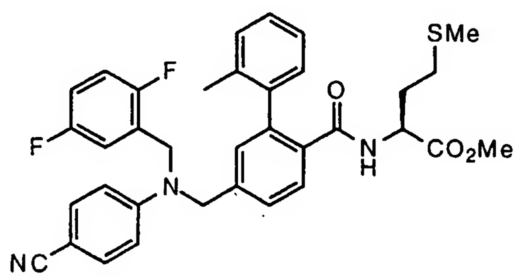
Compound 1003C was prepared in the same fashion as 997D (93% yield).

^{1}H NMR (d_6-DMSO):δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.80-2.11 (comp, 8 H), 2.41 (s, 3 H), 3.64-3.73 (br, 1 H), 4.82 (s, 2 H), 4.87 (s, 2 H), 6.83 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 5.8 Hz, 1 H), 7.04 (s, 1 H), 7.08-7.37 (comp, 11 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.76-7.82 (comp, 4 H). HR
MS (FAB): $(M•)^+$ calc for $C_{41}H_{38}N_3O_3S_2$: 685.2433; found: 685.2421 (-1.8 ppm error).



Example 1004

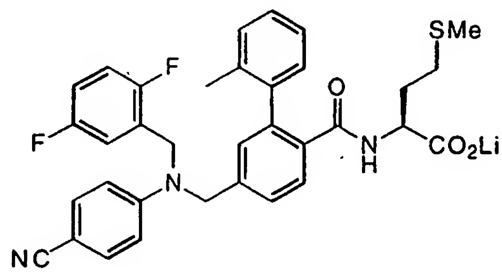
N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt



Example 1004A

A heterogeneous mixture of 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) (0.638 g, 2.00 mmol), 4-aminobenzonitrile (0.241 g, 2.0 mmol), K_2CO_3 (1.11 g, 8.00 mmol), and tetrabutylammonium iodide (0.0754 g, 0.200 mmol) in acetonitrile solvent (5 mL) was heated to 70 °C for 18 h. Next, 2,5-difluorobenzyl bromide (0.507 g, 2.40 mmol) was added, and the reaction mixture was returned to 70 °C. After 16 h the reaction mixture was cooled to room temperature, diluted with DMF solvent (5 mL) and treated with solid LiOH (0.514 g, 12.0 mmol), and then heated to 90 °C for 14 h. The reaction mixture was cooled to room temperature and diluted with additional DMF (20 mL). Triethylamine hydrochloride (1.40 g, 10.0 mmol) was added, followed by methionine methyl ester hydrochloride (0.807 g, 4.00 mmol), 3-hydroxy-1,2,3-benzotriazin-4(3H)-one (HOOBT) (1.66 g, 10.0 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.96 g, 10.0 mmol), and finally, triethylamine (1.02 g, 10.0 mmol). The mixture was

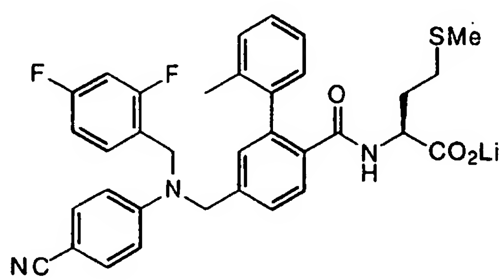
heated to 60 °C for 8 h, cooled to room temperature, diluted with ethyl acetate (80 mL), and extracted with 2:1:1 H_2O: saturated aqueous $NaHCO_3$: brine (50 mL + 2 x 20 mL), followed by brine (10 mL). The organic layer was dried over $MgSO_4$, filtered through silica gel with 1:1 hexane: ethyl acetate rinses, and concentrated under reduced pressure to yield an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 70:30 to 50:50 afforded 0.142 g of 1004A as a colorless oil (12% yield). ^1H NMR ($CDCl_3$):δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.96 (m, 1 H), 6.69 (d, J = 9.0 Hz, 2 H), 6.78-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{35}H_{34}F_2N_3O_3S$: 614; found: 614. LR MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{32}F_2N_3O_3S$: 612; found: 612.



Example 1004B

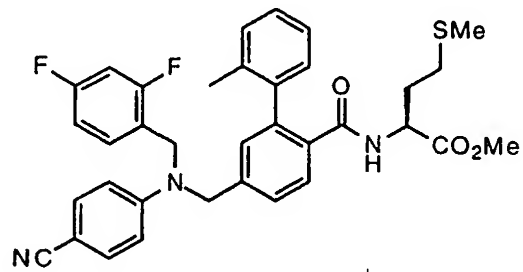
N-[4-N-2,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

Compound 1004B was prepared in the same fashion as 997D (93% yield). ^1H NMR (d_6-DMSO):δ 1.50-1.80 (comp, 2 H), 1.90-2.12 (comp, 8 H), 3.64-3.81 (m, 1 H), 4.84-5.00 (comp, 4 H), 6.75-6.88 (comp, 2 H), 6.89-7.08 (comp, 3 H), 7.11-7.40 (comp, 6 H), 7.48-7.63 (comp, 3 H). HR MS (FAB): $(M+H)^+$ calc for $C_{34}H_{32}F_2N_3O_3S$: 600.2132; found: 600.2139 (1.1 ppm error).



Example 1005

N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt



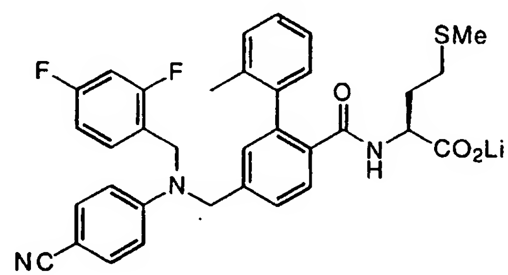
Example 1005A

Compound 1005A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (14% yield).

^{1}H NMR ($CDCl_3$):δ 1.53-1.66 (m, 1 H), 1.80-1.92 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.67 (m, 1 H), 4.71 (s, 2 H), 4.75 (s, 2 H), 5.86-5.92 (m, 1 H), 6.69 (d, J = 9.0 Hz, 2 H), 6.79-6.89 (comp, 2 H), 7.00 (s, 1 H), 7.04-7.37 (comp, 6 H), 7.44 (d, J = 9.0 Hz, 2 H), 7.93 (dd, J = 8.1, 13.5 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{35}H_{34}F_2N_3O_3S$: 614; found: 614. LR

MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{32}F_2N_3O_3S$: 612; found: 612.



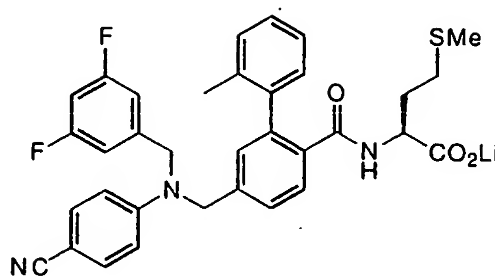
Example 1005B

N-[4-N-2,4-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

Compound 1005B was prepared in the same fashion as 997D (80% yield).

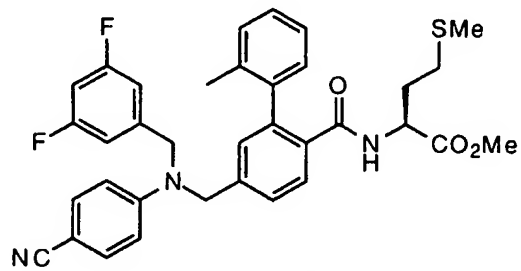
^{1}H NMR (d_6-DMSO):δ 1.48-1.62 (m, 1 H), 1.62-1.73 (m, 1 H), 1.89-2.07 (comp, 8 H), 3.62-3.72 (br, 1 H), 4.82-4.88 (comp, 4 H), 6.79 (d, J = 9.1 Hz, 2 H), 6.90-7.32 (comp, 10 H), 7.48-7.54 (comp, 3 H). HR

MS (FAB): $(M+H)^+$ calc for $C_{34}H_{32}F_2N_3O_3S$: 600.2132; found: 600.2144 (2.0 ppm error).



Example 1006

N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt



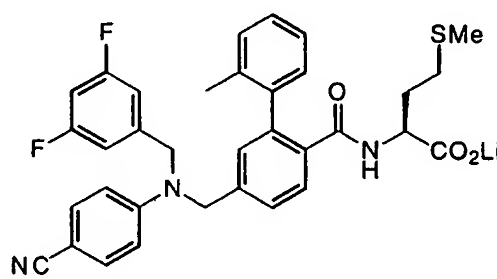
Example 1006A

Compound 1006A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (28% yield).

^{1}H NMR ($CDCl_3$):δ 1.53-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.98-2.12 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.66 (m, 1 H), 4.67 (s, 2 H), 4.76 (s, 2 H), 5.88 (d, J = 7.2 Hz, 1 H), 6.64-6.76 (comp, 5 H), 7.00 (d, J = 1.3 Hz, 1 H), 7.13-7.36 (comp, 5 H), 7.44 (d, J = 8.8 Hz, 2 H), 7.94 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{35}H_{34}F_2N_3O_3S$: 614; found: 614. LR

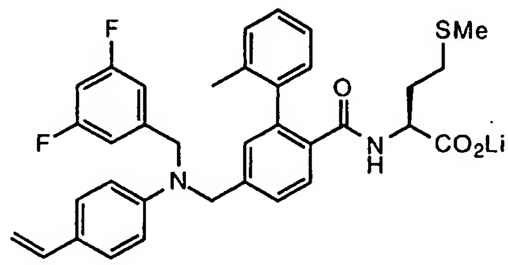
MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{32}F_2N_3O_3S$: 612; found: 612.



Example 1006B

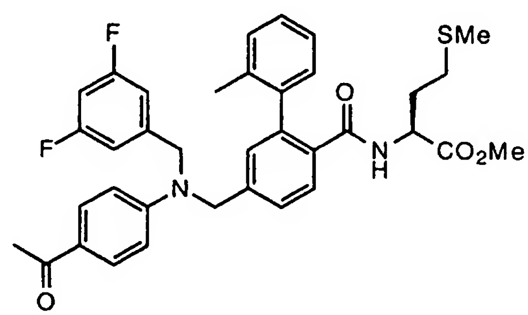
N-[4-N-3,5-difluorobenzyl-N-(4-cyanophenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

Compound 1006B was prepared in the same fashion as 997D (82% yield). ^{1}H NMR (d_6-DMSO):δ 1.48-1.75 (comp, 2 H), 1.90-2.07 (comp, 8 H), 3.66-3.76 (br, 1 H), 4.86 (s, 2 H), 4.92 (s, 2 H), 6.76 (d, J = 8.8 Hz, 2 H), 6.92-7.00 (comp, 4 H), 7.07-7.24 (comp, 5 H), 7.30 (dd, J = 1.5, 8.12 Hz, 1 H), 7.50-7.55 (comp, 3 H). HR MS (FAB): $(M+H)^+$ calc for $C_{34}H_{32}F_2N_3O_3S$: 600.2132; found: 600.2140 (1.2 ppm error).



Example 1007

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

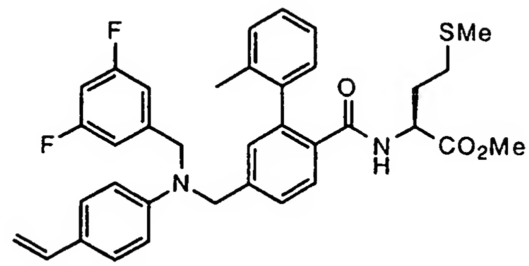


Example 1007A

Compound 1007A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (11% yield).

^{1}H NMR ($CDCl_3$):δ 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.95-2.12 (comp, 8 H), 2.50 (s, 3 H), 3.67 (s, 3 H), 4.56-4.67 (m, 1 H), 4.70 (s, 2 H), 4.78 (s, 2 H), 5.89 (dd, J = 2.5, 7.7 Hz, 1 H), 6.65-6.77 (comp, 5 H), 7.04 (s, 1 H), 7.13-7.36 (comp, 5 H), 7.83 (d, J = 9.2 Hz, 2 H), 7.94 (dd, J = 8.1, 13.8 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{36}H_{37}F_2N_2O_4S$: 631; found: 631. LR

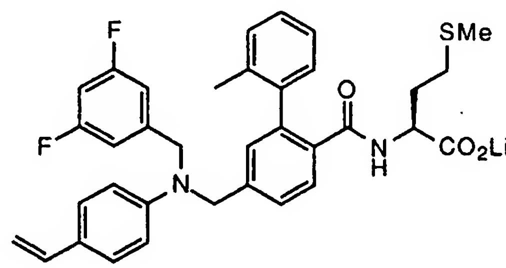
MS (ESI-): $(M\text{-}H)^-$ calc for $C_{36}H_{35}F_2N_2O_4S$: 629; found: 629.



Example 1007B

A solution of 1007A (0.147 g, 0.233 mmol) in 1:1 tetrahydrofuran: methanol solvent (2 mL) was treated with $NaBH_4$ (0.0315 g, 0.815 mmol). After 1 h the mixture was quenched by the addition of H_2O (2 mL), followed by a few drops of 3 M HCl. The reaction mixture was then extracted with ethyl acetate (4 x 2 mL), and the combined organic extracts were rinsed with brine (1 mL), dried over $MgSO_4$, filtered through silica gel with ethyl acetate rinses, and concentrated under reduced pressure to afford an amber oil. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 60:40 to 30:70 afforded 0.0097 g of 1007B as a colorless oil (6.8% yield).

^1H NMR ($CDCl_3$):δ 1.52-1.62 (comp, 2 H), 1.80-1.91 (m, 1 H), 1.99-2.14 (comp, 8 H), 3.66 (s, 3 H), 4.58-4.66 (comp, 3 H), 4.70 (s, 2 H), 5.04 (d, J = 11.1 Hz, 1 H), 5.53 (d, J = 17.6 Hz, 1 H), 5.84-5.90 (m, 1 H), 6.55-6.67 (comp, 3 H), 6.67-6.79 (comp, 2 H), 7.05 (s, 1 H), 7.23-7.34 (comp, 8 H), 7.92 (dd, J = 8.1, 13.6 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{36}H_{37}F_2N_2O_3S$: 615; found: 615. LR MS (ESI-): $(M\text{-}H)^-$ calc for $C_{36}H_{35}F_2N_2O_3S$: 613; found: 613.



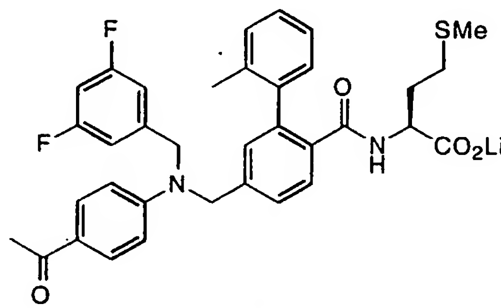
Example 1007C

N-[4-N-3,5-difluorobenzyl-N-(4-vinylphenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

Compound 1007C was prepared in the same fashion as 997D (72% yield).

^1H NMR (d_6-DMSO):δ 1.60-1.70 (br m, 1 H), 1.70-1.83 (br m, 1 H), 1.88-2.06 (br comp, 8 H), 3.58-3.68 (br, 1 H), 4.65-4.77 (br comp, 1 H), 4.75 (s, 2 H), 4.81 (s, 2 H),

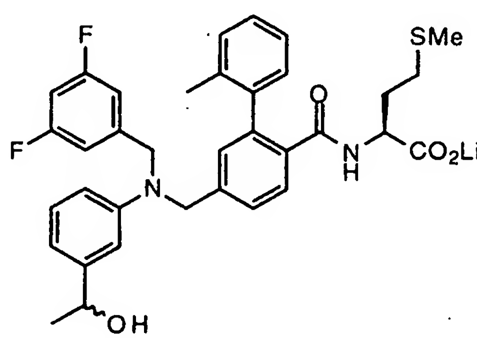
4.96 (d, J = 11.0 Hz, 1 H), 5.51 (dd, J = 1.2, 17.7 Hz, 1 H), 6.54 (dd, J = 11.0, 17.7 Hz, 1 H), 6.65 (d, J = 9.2 Hz, 2 H), 6.89-7.00 (comp, 4 H), 7.01-7.22 (comp, 4 H), 7.23 (d, J = 9.2 Hz, 2 H), 7.30-7.33 (m, 1 H), 7.51 (d, J = 7.9 Hz, 1 H). LR MS (ESI-): $(M-H)^-$ calc for $C_{35}H_{32}F_2LiN_3O_3S$: 599; found: 599.



1008

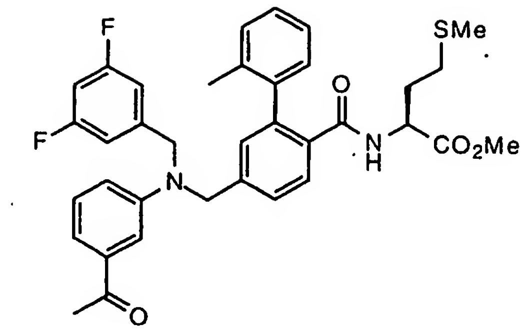
N-[4-N-3,5-difluorobenzyl-N-(4-acetylphenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt

Compound 1008 was prepared in the same fashion as 997D (86% yield).
^1H NMR (d_6-DMSO):δ 1.46-1.61 (m, 1 H), 1.61-1.73 (m, 1 H), 1.86-2.08 (comp, 8 H), 2.38 (s, 3 H), 3.58-3.68 (br, 1 H), 4.85 (s, 2 H), 4.90 (s, 2 H), 6.73 (d, J = 9.0 Hz, 2 H), 6.90-7.00 (comp, 5 H), 7.05-7.20 (comp, 5 H), 7.30 (dd, J = 1.7, 7.8 Hz, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.74 (d, 9.0 Hz, 2 H). HR MS (FAB): $(M+H)^+$ calc for $C_{35}H_{35}F_2N_2O_4S$: 617.2286; found: 617.2277 (-1.5 ppm error).



Example 1009

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl) benzoyl]methionine, lithium salt



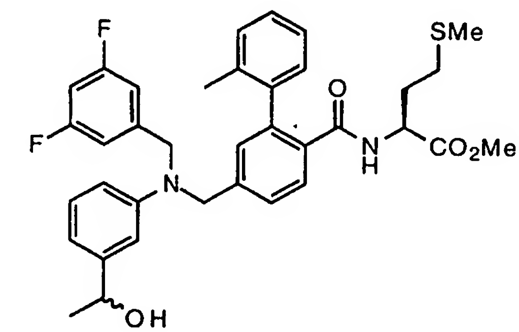
Example 1009A

Compound 1009A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (17% yield).

^{1}H NMR ($CDCl_3$):δ 1.52-1.65 (m, 1 H), 1.79-1.91 (m, 1 H), 2.00-2.14 (comp, 8 H), 2.52 (s, 3 H), 2.67 (s, 3 H), 4.56-4.66 (m, 1 H), 4.66 (s, 2 H), 4.74 (s, 2 H), 5.85-5.91 (m, 1 H), 6.64-6.81 (comp, 3 H), 6.86 (d, J = 8.1 Hz, 1 H), 7.05 (s, 1 H), 7.14-7.35 (comp, 8 H), 7.92 (dd, J = 8.1, 14.0 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{36}H_{37}F_2N_2O_4S$: 631; found: 631. LR

MS (ESI-): $(M-H)^-$ calc for $C_{36}H_{35}F_2N_2O_4S$: 629; found: 629.



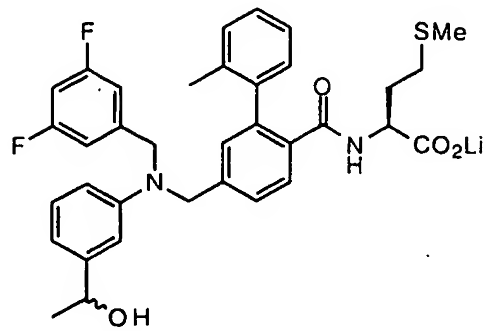
Example 1009B

Compound 1009B was prepared in the same fashion as 1007B (10% yield).

^{1}H NMR ($CDCl_3$):δ 1.41 (d, J = 6.5 Hz, 3 H), 1.52-1.65 (comp, 2 H), 1.77 (d, J = 2.7 Hz, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.15 (comp, 8 H), 3.66 (s, 3 H), 4.56-4.65 (comp, 3 H), 4.69 (s, 2 H), 4.73-4.82 (m, 1 H), 5.85-5.91 (m, 1 H), 6.59 (dd, J = 2.4, 8.2 Hz, 1 H), 6.64-6.80 (comp, 5 H), 7.06 (d, J = 1.3 Hz, 1 H), 7.15-7.19 (m, 1 H), 7.21-7.36 (comp, 5 H), 7.92 (dd, J = 8.1, 14.3 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{36}H_{39}F_2N_2O_4S$: 633; found: 633. LR

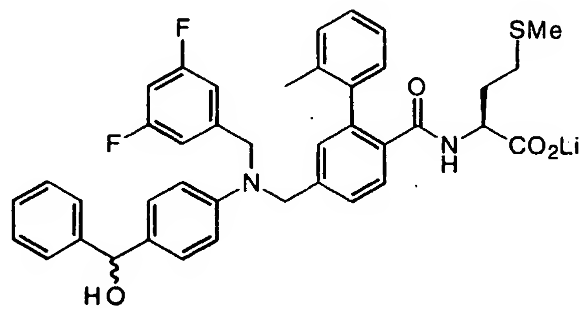
MS (ESI-): $(M-H)^-$ calc for $C_{36}H_{37}F_2N_2O_4S$: 631; found: 631.



Example 1009C

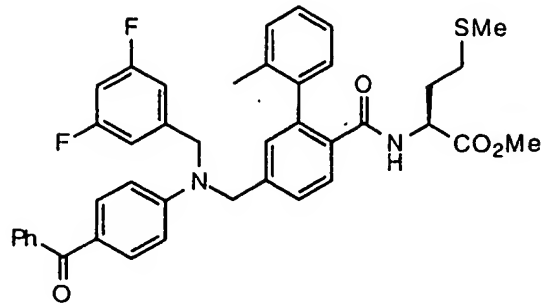
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1009C was prepared in the same fashion as 997D (76% yield). ^{1}H NMR (d_6-DMSO):δ 1.18 (d, J = 6.1 Hz, 3 H), 1.47-1.60 (m, 1 H), 1.60-1.73 (m, 1 H), 1.88-2.09 (comp, 8 H), 3.59-3.68 (m, 1 H), 4.89-4.57 (m, 1 H), 4.71 (s, 2 H), 4.78 (s, 2 H), 4.99 (d, J = 4.1 Hz, 1 H), 6.50 (dd, J = 2.3, 8.4 Hz, 1 H), 6.61 (d, J = 7.4 Hz, 1 H), 6.70 (s, 1 H), 6.89-7.03 (comp, 4 H), 7.03-7.21 (dd, J = 1.3, 7.8 Hz, 1 H), 7.51 (d, J = 9.8 Hz, 1 H). HR MS (FAB): $(M+H)^+$ calc for $C_{35}H_{36}F_2N_3O_4S$: 618.2364; found: 618.2366 (0.4 ppm error).



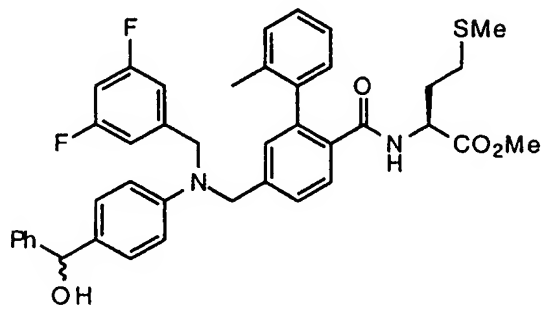
Example 1010

N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



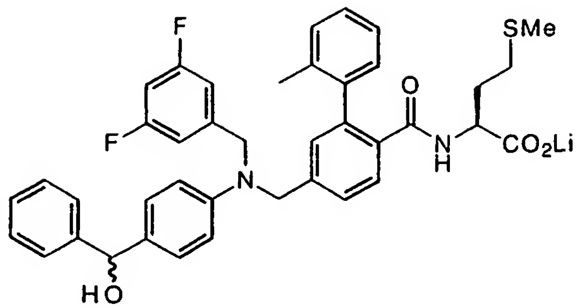
Example 1010A

Compound 1010A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 997B) in the same fashion as 1004A (5.4% yield).
^{1}H NMR (CDCl$_3$):δ 1.53-1.66 (m, 1 H), 1.80-1.91 (m, 1 H), 2.00-2.13 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.66 (m, 1 H), 4.71 (s, 2 H), 4.79 (s, 2 H), 5.86-5.92 (m, 1 H), 6.68-6.78 (comp, 5 H), 7.05 (d, J = 1.6 Hz, 1 H), 7.14-7.35 (comp, 6 H), 7.40-7.47 (comp, 2 H), 7.49-7.55 (m, 1 H), 7.70-7.77 (comp, 4 H), 7.94 (dd, J = 8.2, 13.3 Hz, 1 H). LR MS (ESI-): (M-H)$^-$ calc for $C_{41}H_{37}F_2N_2O_4S$: 691; found: 691.



Example 1010B

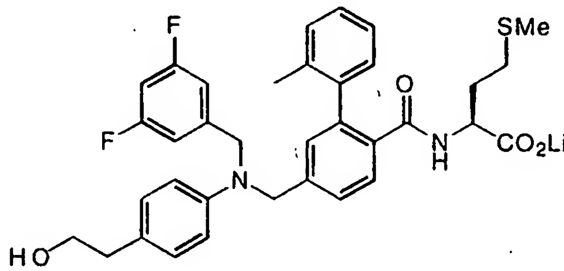
Compound 1010B was prepared in the same fashion as 1007B (6.5% yield).
^{1}H NMR (CDCl$_3$):δ 1.52-1.64 (comp, 2 H), 1.78-1.91 (m, 1 H), 1.99-2.11 (comp, 8 H), 3.66 (s, 3 H), 4.55-4.65 (comp, 3 H), 4.68 (s, 2 H), 5.70 (d, J = 2.9 Hz, 1 H), 5.86 (t, J = 6.4 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 2 H), 6.67-6.72 (m, 1 H), 6.75 (d, J = 6.2 Hz, 2 H), 7.04 (s, 1 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.19-7.41 (comp, 10 H), 7.91 (dd, J = 8.0, 21.3 Hz, 1 H). LR
MS (ESI+): (M-OH)$^+$ calc for $C_{41}H_{39}F_2N_2O_3S$: 677; found: 677. LR
MS (ESI-): (M-H)$^-$ calc for $C_{41}H_{39}F_2N_2O_4S$: 693; found: 693.



Example 1010C

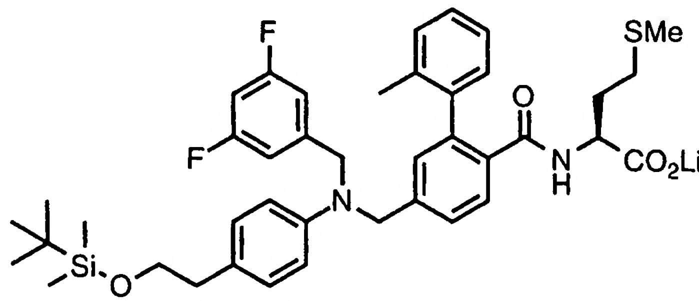
N-[4-N-3,5-difluorobenzyl-N-(4-(1-hydroxy-1-phenylmethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1010C was prepared in the same fashion as 997D (100% yield). ^{1}H NMR (d_6-DMSO):δ 1.50-1.59 (br m, 1 H), 1.62-1.70 (br m, 1 H), 1.88-2.23 (br comp, 8 H), 4.68 (s, 2 H), 4.77 (s, 2 H), 6.66 (d, J = 8.5 Hz, 2 H), 6.92-6.95 (comp, 3 H), 7.02-7.07 (comp, 3 H), 7.11-7.26 (comp, 5 H), 7.27-7.32 (comp, 5 H), 7.49 (d, J = 8.0 Hz, 1 H). LR MS (ESI-): $(M-H)^-$ calc for $C_{40}H_{37}F_2LiN_2O_4S$: 678; found: 678.



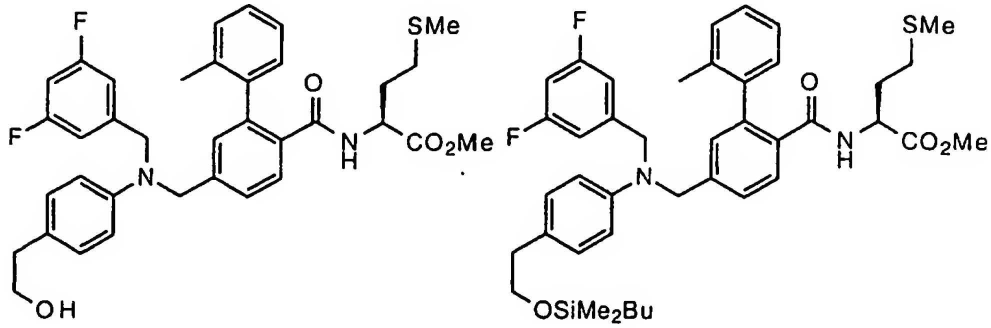
Example 1011

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1012

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1011A and Example 1012A

Compound 1012A was prepared starting from 4-chloromethyl-2-(2-methylphenyl)benzoic acid, methyl ester, 997B, in the same fashion as 1004A (4.1% yield). Compound 1011A was isolated from the crude reaction mixture as a side-product (15% yield).

^{1}H NMR ($CDCl_3$):δ 1.44-1.50 (br, 1 H), 1.52-1.65 (m, 1 H), 1.80-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.76 (t, J = 6.4 Hz, 2 H), 3.66 (s, 3 H), 3.80 (br t, J = 6.4 Hz, 2 H), 4.58-4.68 (comp, 5 H), 5.84-5.90 (m, 1 H), 6.64 (d, J = 8.5 Hz, 2 H), 6.66-6.72 (m, 1 H), 6.77 (d, J = 5.7 Hz, 2 H), 7.04 (d, J = 8.8 Hz, 2 H), 7.07 (s, 1 H), 7.20-7.34 (comp, 5 H), 7.91 (dd, J = 8.2, 13.6 Hz, 1 H). LR

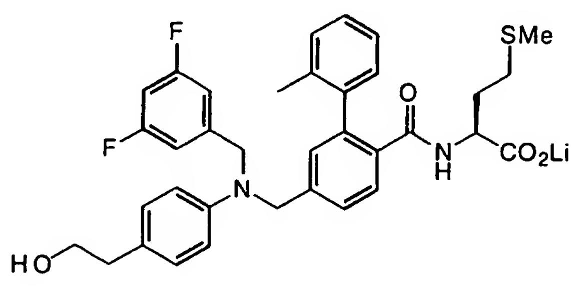
MS (ESI+): $(M+H)^+$ calc for $C_{36}H_{39}F_2N_2O_4S$: 633; found: 633. LR

MS (ESI-): $(M-H)^-$ calc for $C_{36}H_{37}F_2N_2O_4S$: 631; found: 631. 1012A:

^{1}H NMR ($CDCl_3$):δ -0.04 (s, 6 H), 0.86 (s, 9 H), 1.52-1.64 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.12 (comp, 8 H), 2.71 (t, J = 7.2 Hz, 2 H), 3.65 (s, 3 H), 3.73 (t, J = 7.2 Hz, 2 H), 4.56 (s, 2 H), 4.60-4.70 (comp, 3 H), 5.83-5.89 (m, 1 H), 6.62 (d, J = 8.4 Hz, 2 H), 6.65-6.71 (m, 1 H), 6.76 (d, J = 6.1 Hz, 2 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.06 (d, J = 1.7 Hz, 1 H), 7.20-7.34 (comp, 5 H), 7.90 (dd, J = 8.1, 13.2 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{42}H_{53}F_2N_2O_4SiS$: 747; found: 747. LR

MS (ESI-): $(M-H)^-$ calc for $C_{42}H_{51}F_2N_2O_4SiS$: 745; found: 745.

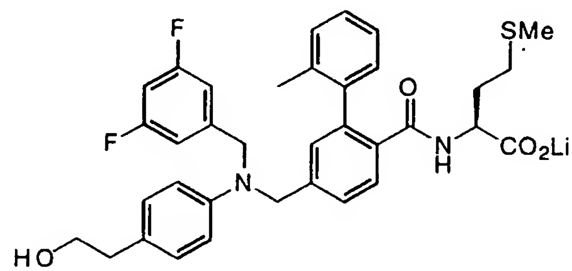


Example 1011B

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1011B was prepared in the same fashion as 997D (76% yield). ^{1}H NMR (d_6-DMSO):δ 1.48-1.74 (br comp, 2 H), 1.90-2.06 (br comp, 8 H), 2.56 (t, J = 7.2 Hz, 2 H), 3.48 (t, J = 7.2 Hz, 2 H), 3.64-3.76 (br, 1 H), 4.69 (s, 2 H), 4.75 (s, 2 H), 6.58 (d, J = 8.5 Hz, 2 H), 6.90-7.22 (br comp, 10 H), 7.30 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 8.1 Hz, 1 H). HR

MS (FAB): $(M+H)^+$ calc for $C_{35}H_{36}F_2LiN_2O_4S$: 625.2524; found: 625.2542 (2.8 ppm error).

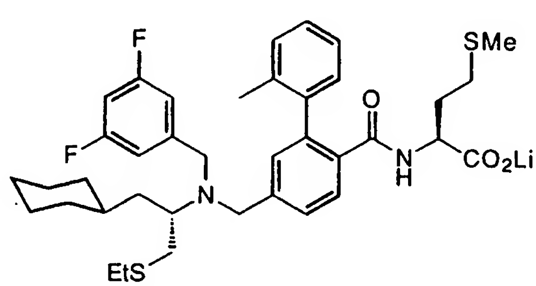


(258473) Example 1012B

N-[4-N-3,5-difluorobenzyl-N-(4-(2-hydroxyethyl)phenyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine, lithium salt

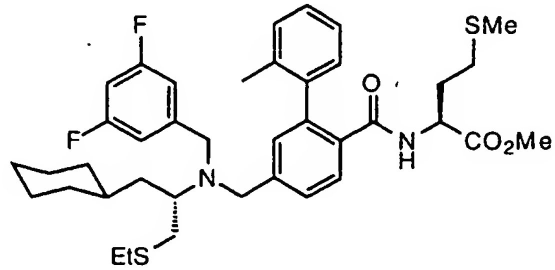
Compound 1012B was prepared in the same fashion as 997D (64% yield). ^{1}H NMR (d_6-DMSO):δ -0.12 (s, 6 H), 0.79 (s, 9 H), 1.48-1.74 (br comp, 2 H), 1.89-2.08 (br comp, 8 H), 2.56 (t, J = 6.9 Hz, 2 H), 3.65 (t, J = 6.9 Hz, 2 H), 4.69 (s, 2 H), 4.76 (s, 2 H), 6.58 (d, J = 8.9 Hz, 2 H), 6.88-7.22 (comp, 10 H), 7.30 (d, J = 7.7 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H). HR

MS (FAB): $(M+H)^+$ calc for $C_{41}H_{50}F_2LiN_2O_4SiS$: 739.3389; found: 739.3389 (0.1 ppm error).



Example 1013

N-[4-*N*-3,5-difluorobenzyl-*N*-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.



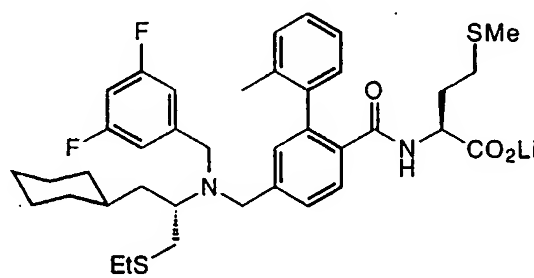
Example 1013A

Compound 1013A was prepared starting from 4-bromomethyl-2-(2-methylphenyl)benzoic acid, methyl ester (example 1178D) in the same fashion as 1004A (10% yield).

^{1}H NMR ($CDCl_3$):δ 0.70-0.93 (comp, 2 H), 1.06-1.71 (comp, 16 H), 1.30-1.92 (m, 1 H), 1.99-2.10 (comp, 7 H), 2.19 (s, 1 H), 2.39-2.48 (comp, 3 H), 2.77-2.89 (comp, 2 H), 3.58-3.71 (comp, 7 H), 4.56-4.70 (m, 1 H), 5.89 (d, J = 7.4 Hz, 1 H), 6.61-6.70 (m, 1 H), 6.94 (d, J = 8.1 Hz, 2 H), 7.15-7.22 (m, 1 H), 7.22-7.37 (comp, 9 H), 7.50 (d, J = 8.1 Hz, 1 H), 7.92 (dd, J = 8.1, 15.1 Hz, 1 H). LR

MS (ESI+): $(M+H)^+$ calc for $C_{39}H_{51}F_2N_2O_3S_2$: 697; found: 697. LR

MS (ESI-): $(M-H)^-$ calc for $C_{39}H_{49}F_2N_2O_3S_2$: 695; found: 695.



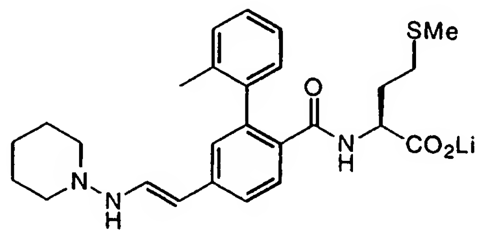
Example 1013B

N-[4-N-3,5-difluorobenzyl-N-(1-ethylthio-3-cyclohexylprop-2-yl)aminomethyl-2-(2-methylphenyl)benzoyl] methionine.

Compound 1013B was prepared in the same fashion as 997D (76% yield).

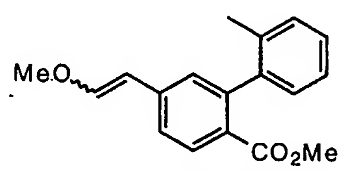
^{1}H NMR (d_6-DMSO):δ 0.59-0.74 (m, 1 H), 0.74-0.91 (m, 1 H), 0.97-1.18 (comp, 4 H), 1.21-1.33 (comp, 2 H), 1.36-1.75 (comp, 8 H), 1.76-1.87 (m, 1 H), 1.88-1.96 (comp, 2 H), 1.96-2.02 (comp, 2 H), 2.15-2.22 (br, 1 H), 2.34-2.45 (comp, 3 H), 2.60-2.70 (br, 1 H), 2.94 (dd, J = 5.9, 12.9 Hz, 1 H), 3.32-3.45 (comp, 4 H), 3.57-3.74 (br comp, 5 H),

6.93 (d, J = 6.3 Hz, 1 H), 7.03-7.25 (comp, 7 H), 7.38 (d, J = 7.3 Hz, 1 H), 7.50 (d, J = 7.7 Hz, 1 H). HR
MS (FAB): $(M+H)^+$ calc for $C_{38}H_{49}F_2N_2O_3S_2$: 683.3153; found: 683.3132 (-3.0 ppm error).



Example 1014

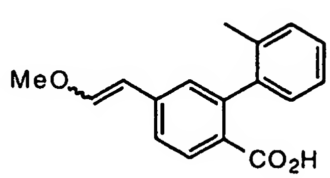
N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt



Example 1014A

A solution of (methoxymethyl)triphenylphosphonium chloride (15.6 g, 45.6 mmol) in tetrahydrofuran solvent (35 mL) was treated with sodium bis(trimethylsilyl)amide (45 mL of a 1 M tetrahydrofuran solution, 45 mmol), and the resulting deep red solution was treated with 4-formyl-2-(2-methylphenyl)benzoic acid, methyl ester, 1332A (7.30 g, 28.7 mmol). After 18 h the reaction mixture was diluted with diethyl ether solvent (100 mL) and filtered through silica gel with additional diethyl ether rinses. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 98:2 to 94:6 afforded 6.62 g of 1014A as a white solid (82% yield).

^1H NMR ($CDCl_3$):δ 2.06 (s, 3 H), 3.59 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer), 5.24 (d, J = 7.1 Hz, 1 H, Z isomer), 5.81 (d, J = 13.2 Hz, 1 H, E isomer), 6.23 (d, J = 7.1 Hz, 1 H, Z isomer), 7.06-7.10 (comp, 2 H), 7.16-7.64 (comp, 5 H), 7.90 (dd, J = 2.3, 8.4 Hz, 1 H). LR
MS (ESI+): $(M+H)^+$ calc for $C_{18}H_{19}O_3$: 283; found: 283.

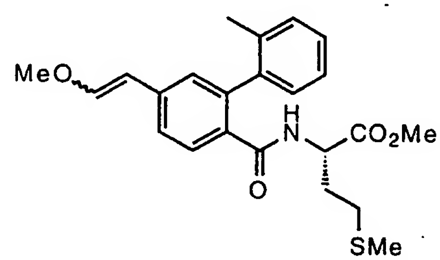


Example 1014B

A solution of 1014A (2.42 g, 8.57 mmol) in saturated methanolic LiOH (10 mL) was heated to reflux for 16 h. The reaction mixture was poured into H_2O (90 mL), and the resulting mixture was extracted with diethyl ether (3 x 30 mL). The aqueous layer was cooled to 0 °C with vigorous stirring and was slowly and carefully neutralized and then acidified to pH 4 by the addition of 3 M HCl. The cloudy solution was extracted with diethyl ether (3 x 30 mL), and the combined organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure to provide 1.81 g of 1014B as a white foam (79% yield). LR

MS (ESI+): $(M+H)^+$ calc for $C_{17}H_{17}O_3$: 269; found: 269. LR

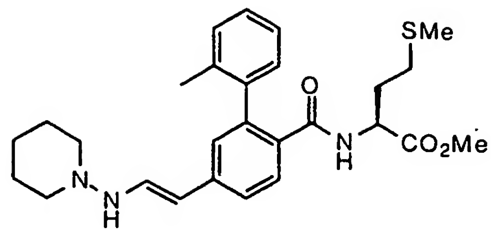
MS (ESI-): $(M-H)^-$ calc for $C_{17}H_{15}O_3$: 267; found: 267.



Example 1014C

A heterogeneous mixture of 1014B (1.81 g, 6.75 mmol), methionine methyl ester hydrochloride (2.72 g, 13.5 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (4.56 g, 33.8 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (6.60 g, 33.8 mmol) in DMF solvent (40 mL) was treated with triethylamine (3.45 g, 33.8 mmol). The mixture was heated to 50 °C for 60 h, cooled to room temperature, diluted with ethyl acetate (200 mL), and extracted with 2:1:1 H_2O: saturated aqueous $NaHCO_3$: brine (200 mL + 2 x 100 mL), followed by brine (50 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure to yield an amber oil. Flash column chromatography eluting with hexane and ethyl acetate using an elution gradient of 80:20 to 70:30 afforded 2.55 g of 1014C as a colorless oil (91% yield).

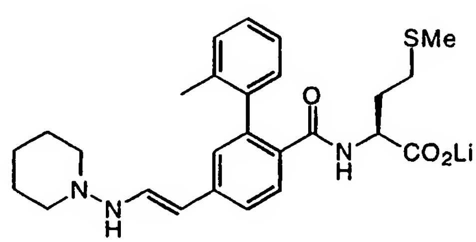
^1H NMR ($CDCl_3$):δ 1.51-1.63 (m, 1 H), 1.79-1.91 (m, 1 H), 1.99-2.21 (comp, 8 H), 3.65 (s, 3 H), 3.70 (s, 3 H, E isomer), 3.79 (s, 3 H, Z isomer), 4.56-4.67 (m, 1 H), 5.24 (d, J = 7.1 Hz, 1 H, E isomer), 5.82 (d, J = 12.9 Hz, 1 H, E isomer), 5.83-5.89 (m, 1 H), 7.00-7.36 (comp, 6 H), 7.12 (d, J = 12.9 Hz, 1 H, E isomer), 7.63-7.96 (comp, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{23}H_{28}O_4S$: 414; found: 414,



Example 1014D

A solution of 1014C (8.0 mL of a 0.1 M dioxane solution, 0.800 mmol) and H_2O (1.6 mL) was treated with p-toluenesulfonic acid hydrate (0.0309 g, 0.160 mmol). After 17 h the mixture was diluted with additional H_2O (12 mL) and then extracted with ethyl acetate (10 mL + 3 x 5 mL). The combined organic extracts were rinsed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure to provide a pale yellow oil. The oil was dissolved in benzene solvent (4 mL) and treated with Na_2SO_4 (0.454 g, 3.20 mmol), followed by 1-aminopiperidine (0.0991 g, 0.960 mmol), resulting in a bright yellow solution. After 18 h the reaction mixture was filtered through silica gel with ethyl acetate rinses and then concentrated under reduced pressure. Radial chromatography eluting with hexane and ethyl acetate using an elution gradient of 70:30 to 30:70 afforded 0.0342 g of 1014D as a colorless oil (8.9% yield).

^{1}H NMR ($CDCl_3$):δ 1.44-1.53 (comp, 2 H), 1.54-1.74 (comp, 5 H), 1.79-1.91 (m, 1 H), 1.99-2.10 (comp, 5 H), 2.18 (s, 1 H), 2.95 (app t, J = 5.6 Hz, 4 H), 3.62-3.67 (comp, 5 H), 4.56-4.67 (m, 1 H), 5.88 (d, J = 7.8 Hz, 1 H), 6.93-6.99 (m, 1 H), 7.06 (s, 1 H), 7.16-7.35 (comp, 6 H), 7.91 (dd, J = 8.2, 15.6 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{27}H_{36}N_2O_3S$: 482; found: 482. LR MS (ESI-): $(M-H)^-$ calc for $C_{27}H_{34}N_3O_3S$: 480; found: 480.



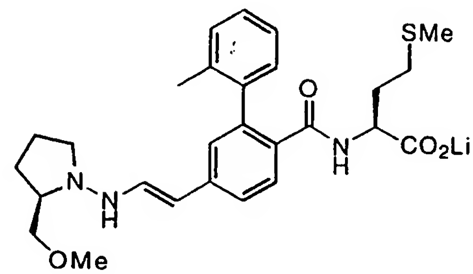
Example 1014E

N-[4-(2-N-piperidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1014E was prepared in the same fashion as 997D (39% yield).

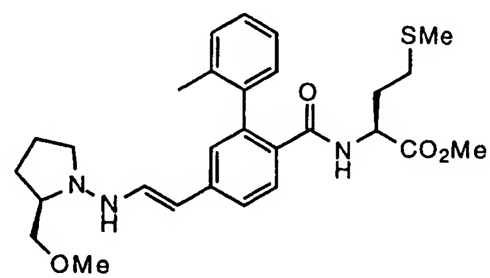
^{1}H NMR (d_6-DMSO):δ 1.36-1.45 (comp, 2 H), 1.50-1.76 (comp, 6 H), 1.76-2.20 (comp, 8 H), 2.84-2.90 (comp, 4 H), 3.53 (d, J = 5.8 Hz, 1 H), 3.62-3.72 (br, 1 H), 6.92 (d, J = 5.8 Hz, 1 H), 6.96-7.03 (comp, 2 H), 7.10-7.24 (comp, 4 H), 7.27 (dd, J = 1.4, 7.8 Hz, 1 H), 7.48 (d, J = 8.1 Hz, 1 H). HR

MS (FAB): $(M+Li)^+$ calc for $C_{26}H_{33}LiN_3O_3S$: 474.2403; found: 474.2386 (-3.6 ppm error).



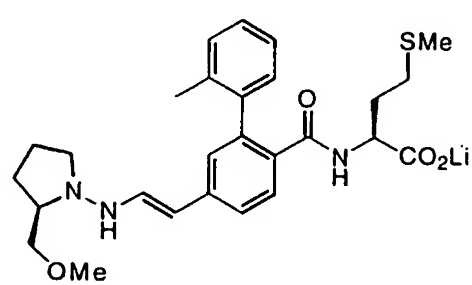
<u>Example 1015</u>

<u>N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt</u>



<u>Example 1015A</u>

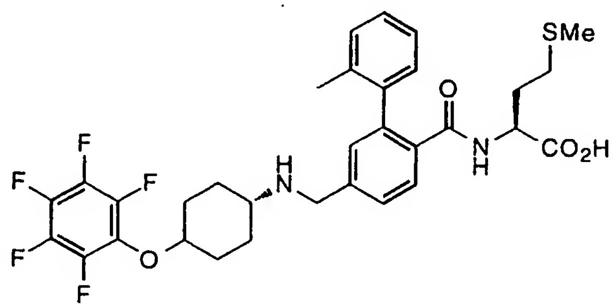
Compound 1015A was prepared in the same fashion as 1014D (11% yield). ^1H NMR ($CDCl_3$): δ 1.52-1.64 (m, 1 H), 1.71-2.20 (comp, 14 H), 2.72-2.84 (m, 1 H), 3.31-3.67 (comp, 12 H), 4.56-4.68 (m, 1 H), 5.88 (d, J = 7.3 Hz, 1 H), 6.64-6.70 (m, 1 H), 7.07 (s, 1 H), 7.17-7.35 (comp, 6 H), 7.91 (dd, J = 7.7, 15.4 Hz, 1 H). LR MS (ESI+): $(M+H)^+$ calc for $C_{28}H_{38}N_3O_4S$: 512; found: 512. LR MS (ESI-): $(M-H)^-$ calc for $C_{28}H_{36}N_3O_2S$: 510; found: 510.



<u>Example 1015B</u>

N-[4-(2-N-2-methoxymethylpyrrolidin-1-ylaminoethenyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

Compound 1015B was prepared in the same fashion as 997D (50% yield). ^{1}H NMR (d_6-DMSO):δ 1.49-1.72 (comp, 3 H), 1.76-2.20 (comp, 10 H), 2.62-2.72 (m, 1 H), 3.19-3.55 (comp, 2 H), 3.62-3.74 (br, 1 H), 6.66 (app t, J = 5.5 Hz, 1 H), 6.89-6.94 (d, J = 5.5 Hz, 1 H), 7.02 (s, 1 H), 7.12-7.30 (comp, 5 H), 7.49 (d, J = 8.1 Hz, 1 H). HR MS (FAB): $(M+Li)^+$ calc for $C_{27}H_{35}LiN_3O_4S$: 504.2508; found: 504.2509 (1.2 ppm error).



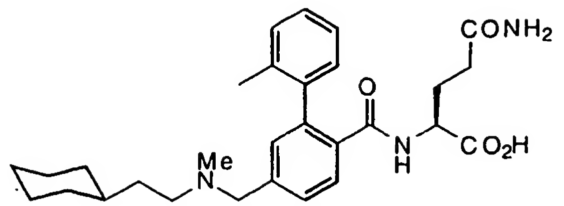
Example 1017

N-[4-N-(4-trans-pentafluorophenoxycyclohexyl)aminomethyl-2-(2-methylphenyl)benzoyl]methionine

A solution of trans-4-aminocylohexanol (3.03 g, 20.0 mmol) and diisopropylethylamine (7.4 mL, 42.0 mmol) in methylene chloride (30 mL) was treated with t-butyl dicarbonate (4.37 g, 20.0 mmol) over 5 minutes. The reaction stirred overnight at room temperature and was washed with 1 M HCl, 5% $NaHCO_3$, and brine to give the Boc-amine in nearly quantitative yield. A portion of this product (215 mg, 1.0 mmol) was combined with hexafluorobenzene (223 mg, 1.2 mmol) and 15-crown-5 (44 mg, 0.2 mmol) in DMF (3 mL) at room temperature. NaH (60% in oil, 4.4 mg, 1.2 mmol was added and stirred overnight. Standard aqueous workup provided 149 mg of the protected pentafluorophenyl ether which was treated with excess TFA in methylene chloride, stripped to dryness, and reductively alkylated and saponified as described previously to provide 160 mg of the title compound.

MS m/e 635 $(M-H)^-$.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.5 (m, 4H), 1.79 (m, 1H), 2.05 (m, 12H), 2.81 (m, 1H), 4.05 (m, 4H), 6.25 (m, 1H), 6.81 (m, 2H), 7.1-7.7 (m, 7H).



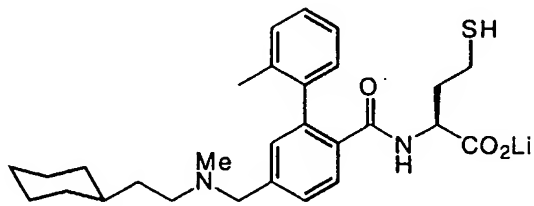
Example 1018

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutamine Trifluoroacetic Acid salt

The compound was made by standard amino acid coupling of 4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid and L-Glu-OtBu followed by treatment with TFA.

MS m/e 492 $(M-H)^-$.

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.1 (m, 4H), 1.63 (m, 9H), 1.9 (m, 3H), 2.1 (m, 3H), 2.71 (s, 3H), 3.1 (m, 2H), 4.09 (m, 1H), 4.29 (m, 1H), 4.43 (m, 1H); 6.74 (s, 1H), 7.1-7.22 (m, 3H), 7.39 (s, 1H), 7.60 (m, 2H), 8.32 (m, 2H), 9.62 (bs, 1H).



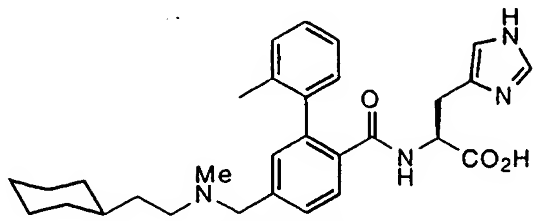
Example 1019

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]homocysteine, lithium salt

Prepared in a manner analogous to Example 1018 using L-homocysteine thiolactone and opening the resulting thiolactone with 1 equivalent of LiOH.

MS m/e 481 $(M-H)^-$.

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.84 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 7H), 3.48 (s, 3H), 3.82 (m, 1H), 3.97 (m, 1H), 6.95 (m, 1H), 7.0-7.34 (m, 4H), 7.5 (m, 1H), 7.65 (m, 1H), 8.39 (m, 1H).



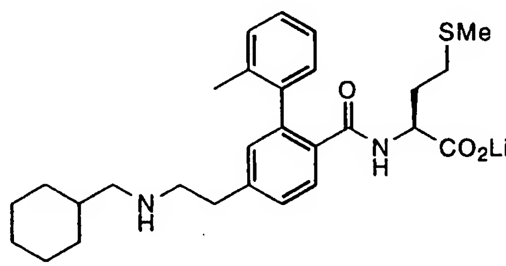
Example 1020

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]histidine Trifloroacetic Acid salt

Prepared in a manner analogous to Example 1018 using L-His(trt)-OMe•HCl, removing the methyl ester with LiOH, and removing the im-trityl group with TFA/triethylsilane.

MS m/e 497 $(M+H)^+$.

^{1}H NMR (d$_6$-DMSO, 300 MHz) δ 0.90 (m, 2H), 1.17 (m, 4H), 1.63 (m, 8H), 1.99 (m, 6H), 2.1 (m, 3H), 2.73 (m, 3H), 3.0 (m, 2H), 4.3 (m, 1H), 4.4 (m, 1H), 4.56 (m, 2H), 7.08 (m, 1H), 7.15-7.42 (m, 3H), 7.58 (m, 2H), 8.62 (m, 1H), 8.97 (s, 1H).



Example 1021

N-[4-(N-cyclohexylmethylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl methionine methyl ester (84 mg, 0.17 mmol) was treated with LiOH (1 M, 85 μL) in methanol to provide the title compound.

MS m/e 481 $(M-H)^-$.

^{1}H NMR (d$_6$-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.36 (m, 1H), 1.62 (m, 9H), 1.98 (m, 10H), 3.7 (m, 2H), 4.27 (m, 1H), 6.90 (m, 1H), 7.00 (m, 1H), 7.1-7.3 (m, 4H), 7.44 (m, 1H), 8.24 (m, 1H).

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl methionine methyl ester

Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate hydrochloride (1.33 g, 3.31 mmol) was treated with sat. LiOH (1.3 mL, 6.95 mmol) in 50 mL methanol at 60 °C until no starting material remained by tlc. The solution was evaporated to dryness and treated with Met-OMe•HCl (0.99 g, 4.96 mmol), EDAC (1.26 g, 6.6 mmol), HOBt (1.5 g, 9.9 mmol), and TEA (to pH 6~7) in 25 mL DMF. Standard aqueous workup followed by flash chromatography (100 % EtOAc) provided 1.5 g of the title compound.

MS m/e 497 $(M-H)^-$.

^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 8H), 2.1 (m, 8H), 2.47 (m, 2H), 2.9 (m, 4H), 3.68 (s, 3H), 4.63 (m, 1H), 5.89 (d, 1H, J = 7 Hz), 7.04 (s, 1H), 7.19 (m, 1H), 7.3 (m, 4H), 7.91 (m, 1H).

<u>Methyl 4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoate</u>

Methyl 4-(propan-3-al)-2-(2-methylphenyl)benzoate (5.0 g, 18.6 mmol) and cyclohexylmethylamine (2.32 g, 10.5 mmol) were dissolved in 250 mL 1 % acetic acid in methanol. After 10 minutes, sodium cyanoborohydride (1.76 g, 28 mmol) was added. The mixture stirred overnight at room temperature before evaporating to dryness. The residue was dissolved in ether and washed with 5 % $NaHCO_3$, water, and brine, dried over Na_2SO_4, and treated with anh. HCl. The oily product was crystalized from methanol and ether.

MS m/e 366 $(M+H)^+$.

^1H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 2H), 1.2 (m, 4H), 1.6 (m, 6H), 2.06 (s, 3H), 2.48 (d, 2H, J = 7 Hz), 2.92 (s, 4H), 3.61 (s, 3H), 7.06 (m, 1H), 7.23 (m, 5H), 7.92 (m, 1H).

<u>Methyl 4-(propan-3-al)-2-(2-methylphenyl)benzoate</u>

Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate (5.23 g, 19.6 mmol), osmium tetroxide (0.02 mmol/mL t-BuOH, 29.5 mL), and sodium periodate (10.5 g, 49.1 mmol) were combined in 200 mL acetone with 50 mL water. After stirring at ambient temperature for 1 hour, the mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4 to give the desired product which was used directly in the next step.

MS m/e 286 $(M+NH_4)^+$.

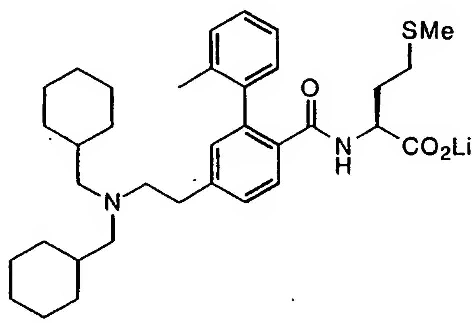
^1H NMR ($CDCl_3$, 300 MHz) δ 2.06 (m, 3H), 3.61 (s, 3H), 3.8 (m, 2H), 7.1 (m, 1H), 7.25 (m, 5H), 7.95 (m, 1H), 9.80 (m, 1H).

<u>Methyl 4-(prop-2-enyl)-2-(2-methylphenyl)benzoate</u>

Methyl 4-iodo-2-(2-methylphenyl)benzoate (10.0 g, 28.4 mmol), allyltributyl tin (11.3 g, 34.1 mmol), and dichlorobis(triphenylphosphine)palladium (II) (1.0 g, 1.42 mmol) were combined in 50 mL toluene and 20 mL NMP and heated at 125 °C for 18 hours. The reaction was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, and chromatographed (5 % EtOAc in hexanes) to provide the title compound in 74 % yield.

MS m/e 284 $(M+NH_4)^+$.

^1H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 3H), 3.45 (d, 2H, J = 7 Hz), 3.61 (s, 3H), 5.1 (m, 2H), 5.97 (m, 1H), 7.08 (m, 1H), 7.23 (m, 5H), 7.94 (m, 1H).



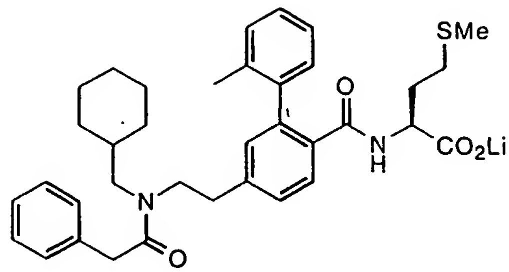
<u>Example 1022</u>

<u>N-[4-(N,N-di-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt</u>

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl methionine methyl ester (300 mg, 0.60 mmol) and cyclohexylcarboxaldehyde (140 mg, 1.21 mmol) were dissolved in 1 % acetic acid in methanol (5 mL) and treated with sodium cyanoborohydride (76 mg, 1.21 mmol). Standard workup followed by flash chromatography (20 % ethyl acetate in hexane) provided 320 mg which was subsequently saponified with LiOH to the title compound.

MS m/e 577 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.75 (m, 4H), 1.10 (m, 8H), 1.30 (m, 2H), 1.61 (m, 9H), 2.0 (m, 10H), 2.6 (m, 2H), 2.7 (m, 2H), 3.3 (m, 1H), 3.68 (m, 1H), 6.90 (m, 2H), 7.1 (m, 5H), 7.44 (m, 1H).



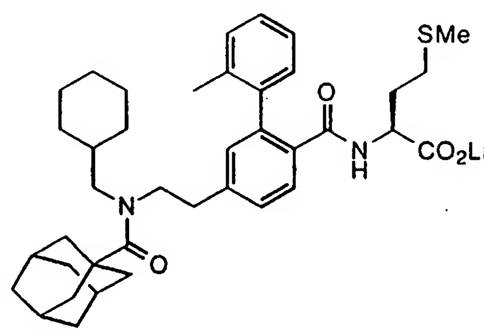
Example 1023

N-[4-(N-cyclohexylmethyl-N-phenylacetylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(cyclohexylmethyl)aminoethyl)-2-(2-methylphenyl)benzoyl methionine methyl ester (75 mg, 0.11 mmol), phenacetyl chloride (26 mg, 0.17 mmol), and triethylamine (17 mg, 0.15 mmol) were stirred in DMF (0.5 mL) for 18 hours at ambient temperature. The reaction was diluted with EtOAc, washed with 5 % $NaHCO_3$, water, and brine, dried over Na_2SO_4, and chromatographed (50 % EtOAc/hexanes) to provide 66 mg of the methyl ester of the title compound. This was subsequently saponified with LiOH in quantitative yield to the title compound.

MS m/e 599 $(M-H)^-$.

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.6 (m, 9H), 1.98 (m, 8H), 2.8 (m, 1H), 3.1 (m, 2H), 3.5 (m, 3H), 3.7 (m, 2H), 7.0 (m, 2H), 7.1-7.3 (m, 9H), 7.45 (m, 1H).



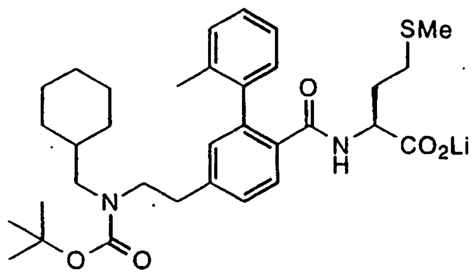
Example 1024

N-[4-(N-cyclohexylmethyl-N-1-adamantanoylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using 1-adamantanecarbonyl chlroide.

MS m/e 643 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.87 (m, 8H), 1.15 (m, 4H), 1.6 (m, 14H), 1.9 (m, 12H), 2.85 (m, 1H), 3.18 (m, 2H), 3.6 (m, 2H), 6.91 (m, 1H), 7.02 (m, 1H), 7.2 (m, 5H), 7.48 (m, 1H).



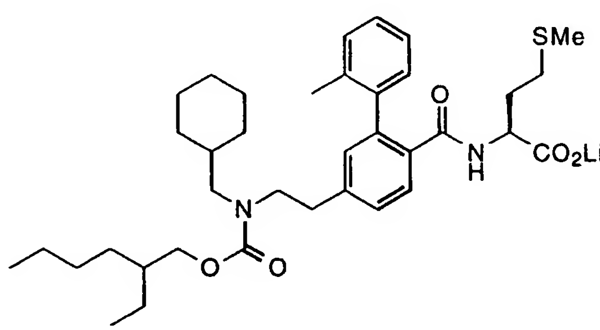
Example 1025

N-[4-(N-cyclohexylmethyl-N-t-butoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using di-t-butyldicarbonate.

MS m/e 581 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.15 (m, 4H), 1.38 (s, 9H), 1.6 (m, 9H), 1.95 (m, 6H), 2.18 (m, 2H), 2.8 (m, 4H), 3.7 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.45 (m, 1H).



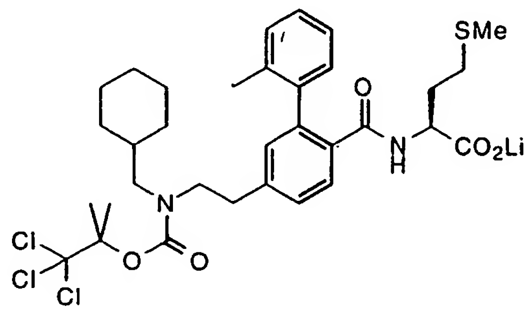
Example 1026

N-[4-(N-cyclohexylmethyl-N-2-ethylhexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using 2-ethylhexyl chloroformate.

MS m/e 637 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 4H), 1.15 (m, 4H), 1.23 (m, 9H), 1.6 (m, 9H), 1.95 (m, 8H), 2.83 (m, 2H), 3.0 (m, 2H), 3.5 (m, 3H), 3.6 (m, 1H), 3.89 (m, 2H), 4.29 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.45 (m, 1H).



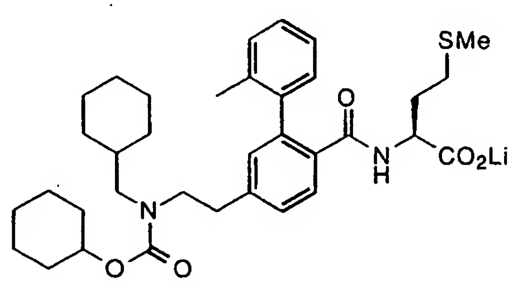
Example 1027

N-[4-(N-cyclohexylmethyl-N-2,2,2-trichloroethoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 683 (M-H)⁻.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.84 (m, 2H), 1.17 (m, 4H), 1.6 (m, 5H), 1.9 (m, 14H), 2.9 (m, 3H), 3.03 (m, 1H), 3.5 (m, 3H), 3.6 (m, 1H), 4.28 (m, 1H), 6.9 (m, 1H), 7.0 (m, 2H), 7.2 (m, 5H), 7.45 (m, 1H).



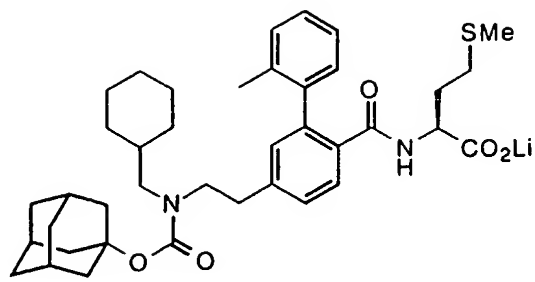
Example 1028

N-[4-(N-cyclohexylmethyl-N-cyclohexyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 607 (M-H)⁻.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.84 (m, 4H), 1.17 (m, 4H), 1.3 (m, 6H), 1.6 (m, 10H), 1.95 (m, 8H), 2.17 (m, 1H), 2.9 (m, 4H), 3.6 (m, 1H), 4.53 (m, 1H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.47 (m, 1H).



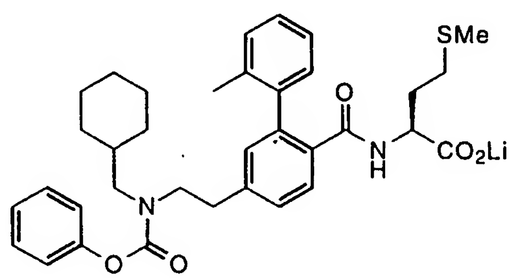
Example 1029

N-[4-(N-cyclohexylmethyl-N-adamantyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 659 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.16 (m, 6H), 1.6 (m, 13H), 2.0 (m, 12H), 2.82 (m, 3H), 2.95 (m, 1H), 3.65 (m, 2H), 6.95 (m, 2H), 7.2 (m, 5H), 7.47 (m, 1H).



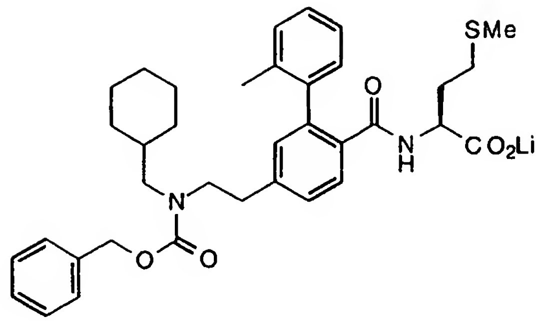
Example 1030

N-[4-(N-cyclohexylmethyl-N-phenoxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 601 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.91 (m, 2H), 1.19 (m, 4H), 1.63 (m, 9H), 1.98 (m, 6H), 2.15 (m, 2H), 2.97 (m, 1H), 3.11 (m, 1H), 3.5 (m, 1H), 3.7 (m, 2H), 6.85-7.39 (m, 12H), 7.48 (m, 1H).



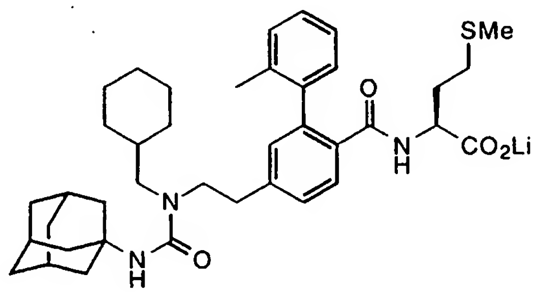
Example 1031

N-[4-(N-cyclohexylmethyl-N-benzyloxycarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023.

MS m/e 615 (M-H)$^-$.

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 2H), 1.13 (m, 4H), 1.6 (m, 6H), 1.95 (m, 6H), 2.14 (m, 2H), 2.83 (m, 2H), 2.99 (m, 2H), 3.40 (m, 2H), 3.65 (m, 2H), 5.04 (m, 2H), 6.9-7.3 (m, 12H), 7.43 (m, 1H).



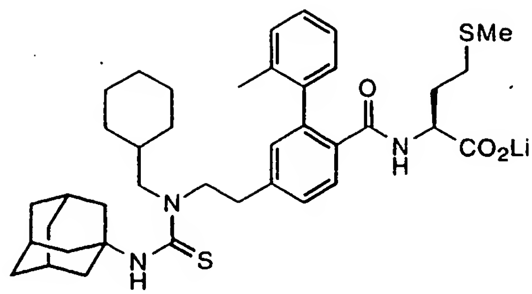
Example 1032

N-[4-(N-cyclohexylmethyl-N-adamant-1-aminocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using adamantyl isocyanate.

MS m/e 658 (M-H)$^-$.

^{1}H NMR (d_6-DMSO, 300 MHz) δ 0.83 (m, 6H), 1.13 (m, 6H), 1.6 (m, 13H), 1.95 (m, 12H), 2.18 (m, 1H), 2.79 (m, 2H), 2.91 (m, 2H), 3.65 (m, 2H), 6.9 (m, 1H), 7.0 (m, 1H), 7.2 (m, 5H), 7.46 (m, 1H).



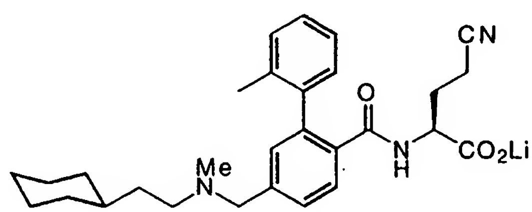
Example 1033

N-[4-(N-cyclohexylmethyl-N-adamant-1-aminothiocarbonylaminoethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

This compound was prepared in a manner analogous to Example 1023 using adamantyl isothiocyanate.

MS m/e 674 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.85 (m, 6H), 1.15 (m, 6H), 1.6 (m, 13H), 2.0 (m, 12H), 2.2 (m, 1H), 2.74 (m, 2H), 2.91 (m, 2H), 3.62 (m, 2H), 6.9-7.5 (m, 8H).



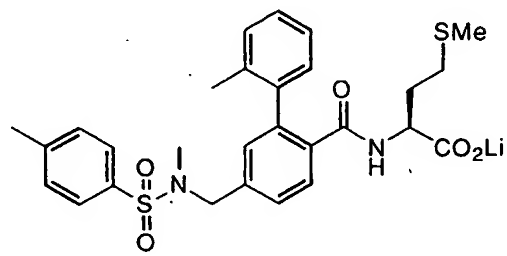
Example 1041

N-[4-(N-(2-cyclohexylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]glutaminitrile, lithium salt

Boc-Gln (2.0 g, 8.11 mmol) and acetic anhydride (0.92 mL, 9.7 mmol) were combined in dry pyridine (10 mL) and stirred at room temperature overnight. The solution was evaporated to dryness and partitioned between EtOAc and 10 % citric acid. The organic layer was washed with 10 % citric acid, water, and brine, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in MeOH (5 mL) and treated with trimethylsilyldiazomethane (2.0 M in hexanes, excess). The mixture was evaporated and chromatographed (50 % EtOAc in hexanes) to give 0.92 g of Boc-glutaminitrile methyl ester. The nitrile (0.24 g, 1 mmol) was treated with excess 50 % trifluoroacetic acid in methylene choride, evaporated and coupled to 4-(2-cyclohexylethyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid via standard techniques, followed by standard lithium hydroxide saponification to provide the title compound.

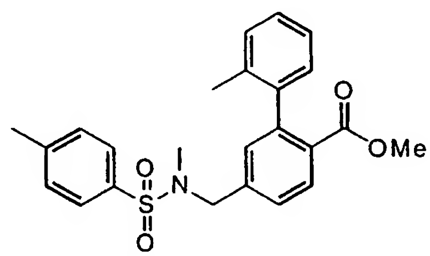
MS m/e 474 $(M-H)^-$.

^1H NMR (d_6-DMSO, 300 MHz) δ 0.82 (m, 2H), 1.11 (m, 3H), 1.32 (m, 5H), 1.6 (m, 7H), 2.18 (m, 6H), 2.32 (m, 1H), 2.58 (m, 1H), 2.75 (m, 1H), 3.53 (m, 2H), 6.9-7.5 (m, 7H), 7.83 (m, 1H).



Example 1047

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

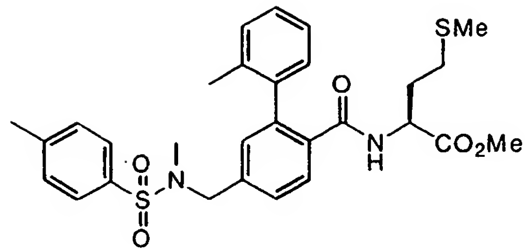


Example 1047A

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

To a solution of N-methyl-p-toluenesulfonamide (203mg) and 4-hydroxymethyl-2-(2-methylphenyl)benzoic acid methyl ester (example 1178C, 255mg) in THF (3mL) at 0°C was added triphenylphosphine (315mg) and diethyl azodicarboxylate (0.19mL). The reaction was warmed, and stirred at ambient temperature for 30h. The reaction was concentrated, and the residue was purified by silica gel chromatography eluting with a gradient from 20% EtOAc/hexane to 100% EtOAc. The product was isolated as a colorless oil (170mg, 40%).

MS (DCI/NH_3) 441 $(M+NH_4)^+$.

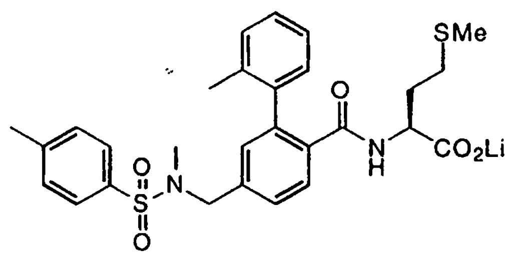


Example 1047B

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D.

MS (APCI(+) m/e $(M+H)^+$ 555,
MS (APCI(-) m/e $(M-H)^-$ 553.



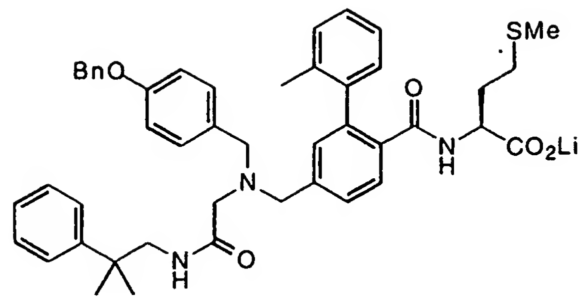
Example 1047C

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-p-Toluenesulfonyl-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

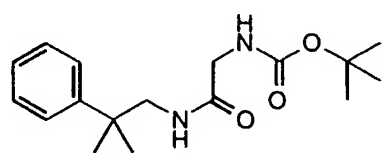
^{1}H NMR (300 MHz, DMSO) δ 1.50-1.88 (m, 4H), 1.92 (s, 3H), 1.95-2.14 (m, 3H), 2.41 (s, 3H), 2.59 (s, 3H), 3.58-3.70 (m, 1H), 4.18 (s, 2H), 6.96 (brd, J=5.4 Hz, 1H), 7.02-7.26 (m, 5H), 7.35 (d, J=8.1 Hz, 1H), 7.44 (d, J=7.8 Hz, 2H), 7.52 (d, J=8.1 Hz, 1H), 7.72 (d, J=7.8 Hz, 2H).

MS (ESI(-)) m/e 539 (M-H); Analysis calc'd for $C_{28}H_{31}LiN_2O_5S_2 \cdot 1.50H_2O$: C, 58.63; H, 5.97; N, 4.88; found: C, 58.61; H, 5.66; N, 4.51.



Example 1048

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

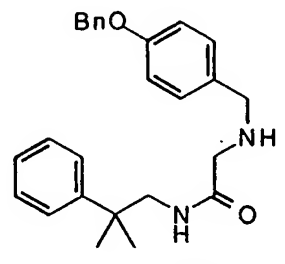


Example 1048A

N-(2-Methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide

To a slurry of NaH (10g of a 60% dispersion in mineral oil) in dry THF (300mL) was added benzylcyanide (10g) by means of a dropping funnel. Cautious addition of methyl iodide (13mL) caused rapid gas evolution and an increase in temperature which was moderated with an ice bath. After stirring at ambient temperature for 12h, the reaction was quenched cautiously with water (100mL). The mixture was diluted with ether (500mL) and the layers were separated. The ether layer was washed with water (100mL) containing a small amount of Na_2SO_3 to eliminate the iodine color, then washed with brine (50mL). The organic solution was dried ($MgSO_4$), filtered and concentrated to afford an oil. This material was added neat to a solution of 1M $LiAlH_4$ (85mL, THF) in ether (100mL). If necessary, the reduction was initiated after a small amount of starting material was added by warming with a heat gun. The starting material was then added at a rate which maintained a gentle reflux. After addition was complete, the reaction was stirred without heating or cooling for 1h. The reaction was cautiously quenched with vigorous stirring by the addition of water (3.2mL), 15%NaOH (3.2mL), and more water (10mL). The suspension was filtered through celite, which was rinsed with ether. The filtrate was concentrated to give an oil (ca. 20g) which contained mineral oil from the sodium hydride dispersion. A portion of this material (3.3g) was dissolved in DMF (67mL) along with N-(tert-butoxycarbonyl)glycine (3.5g), followed by addition of N-methylmorpholine (3.3mL), 1-hydroxybenzotriazole (3.0g), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (5.0g). After stirring at ambient temperature for 15h, the reaction was poured into ether (500mL), washed with water

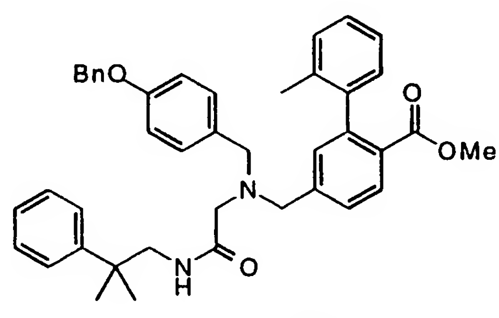
(2X100mL), 1M HCl (2X100mL), saturated $NaHCO_3$ (2X50mL), and brine (100mL). The organic solution was dried ($MgSO_4$), filtered and concentrated to afford a residue which partly solidified. The residue was triturated with hexane, and filtered to give 4.5g of the title compound. MS(DCI/NH_3) 307 $(M+H)^+$.



Example 1048B

N-(2-Methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide

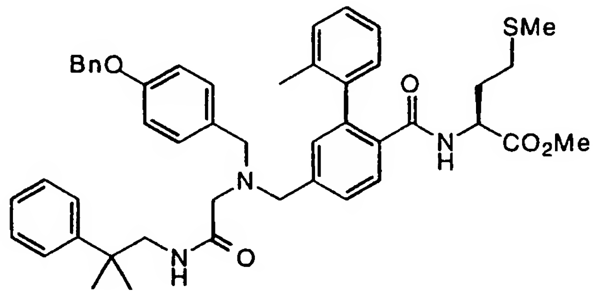
To a solution of N-(2-methyl-2-phenylpropyl)-N-tert-butoxycarbonyl-2-aminoacetamide (4.5g) in dichloromethane (50mL) was added trifluroracetic acid (10mL). After 1.5h at ambient temperature, the reaction was concentrated, then the residue was evaporated from toluene to afford a light tan solid (4.4g). This material was stirred with 4-benzyloxybenzaldehyde (3.27g) in 1:1 THF:EtOH (30mL). Bromcresol green (1mg) was added, and the reaction was adjusted to pH≈3 with 15%NaOH. The reaction was warmed briefly to reflux to complete dissolution of starting material, then cooled to ambient temperature. Sodium cyanoborohydride (15mL, 1M THF) was added, and the reaction color was held at a light green by addition of a 2:1 ethanol:HCl mixture. After starting aldehyde was consumed (TLC), the reaction was concentrated, dissolved in EtOAc (200mL), and washed with saturated $NaHCO_3$ (2X50mL), water (50mL), and brine (50mL). The organic solution was dried ($MgSO_4$), filtered and concentrated, and the residue was purified by silica gel chromatography to give the title compound (1.96g) along with a significant amound of double alkylation product. MS(ESI) 403 $(M+H)^+$.



Example 1048C

4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

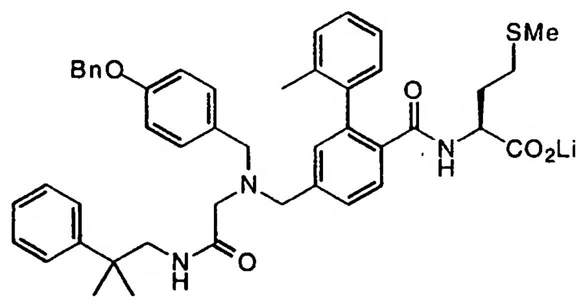
The title compound was prepared by the procedure in example 608B, replacing N-methylcyclohexylethylamine with N-(2-methyl-2-phenylpropyl)-N-(4-benzyloxybenzyl)-2-aminoacetamide. MS(APCI(+)) 641 $(M+H)^+$. MS(APCI(-)) 675 $(M+Cl)^-$.



Example 1048D

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

4-(N-(4-Benzyloxybenzyl)-N-(N-(2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester was converted to the title compound according to the procedures in examples 608C and D. MS(APCI(+)) 772 $(M+H)^+$. MS(APCI(-)) 806 $(M+Cl)^-$.



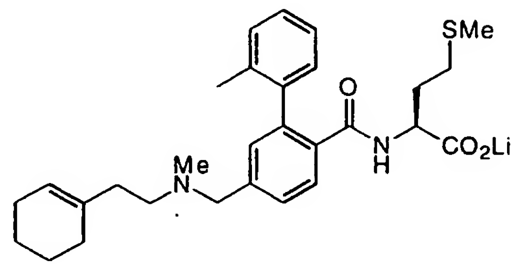
Example 1048E

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-2-methyl-2-phenylpropylacetamido)aminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(4-Benzyloxybenzyl)-N-(N-(2-methyl-2-phenylpropylamino)acetylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted to the title compound by the procedure in example 608E. The product was isolated as a white powder.

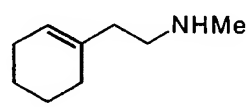
^{1}H NMR (300 MHz, DMSO) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.50-1.84 (m, 5H), 1.92 (s, 3H), 1.95-2.16 (m, 3H), 2.88 (s, 2H), 3.28 (s, 2H), 3.39 (s, 2H), 3.47 (s, 2H), 3.60-

3.68 (m, 1H), 5.07 (s, 2H), 6.87 (d, J=9 Hz, 2H), 6.93 (d, J=9 Hz, 2H), 6.93-7.48 (m, 17H). Analysis calc'd for $C_{46}H_{50}LiN_3O_5S \cdot 1.95H_2O$: C, 69.15; H, 6.80; N, 5.26; found: C, 69.11; H, 6.50; N, 5.13.



Example 1056

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

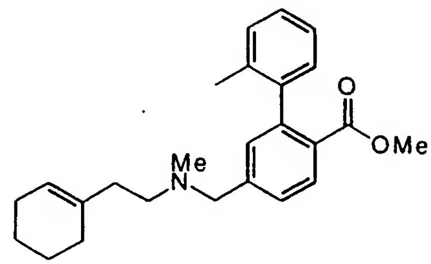


Example 1056A

N-Methyl-2-(1-cyclohexenyl)ethylamine

To a solution of 2-(1-cyclohexenyl)ethylamine (4.0g) in 1,4-dioxane (40mL) was added di-tert-butyldicarbonate (7.7g). After gas evolution ceased (≈2h) the reaction was concentrated. A portion of the residue (2g) was dissolved in THF (10mL) followed by addition of $LiAlH_4$ (10mL, 1M THF), which caused an exotherm. After 3h, more $LiAlH_4$ solution was added (4mL), and the reaction was warmed to reflux. After 1h, the reaction was cooled, and quenched cautiously with vigorous stirring by the addition of water (0.57mL), 1M NaOH (0.6mL), and more water (1.5mL). The suspension was filtered through celite, which was washed with ether. The organic solution was concentrated to give the desired product as a volatile oil (0.8g).

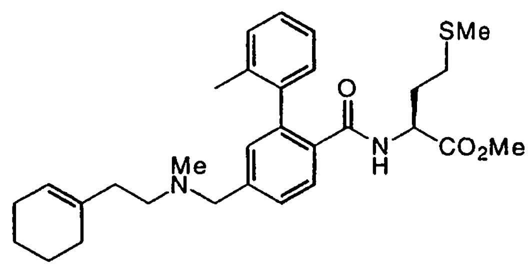
^1H NMR (300 MHz, $CDCl_3$) δ 1.52-1.67 (m, 4H), 1.89-2.04 (m, 4H), 2.14 (brt, J=7 Hz, 2H), 2.42 (s, 3H), 2.63 (t, J=7 Hz, 2H), 5.45 (m, 1H).



Example 1056B

4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid, Methyl Ester

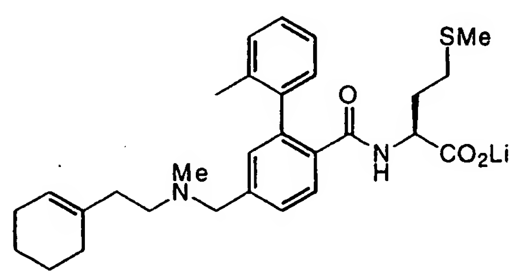
The title compound was prepared from N-methyl-2-(1-cyclohexenyl)ethylamine according to the procedure in example 608B.
MS (DCI/NH_3) 378 $(M+H)^+$.



Example 1056C

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, Methyl Ester

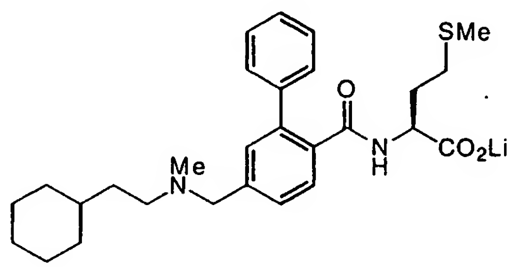
The title compound was prepared from 4-(N-(2-cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoic acid methyl ester according to the procedure in examples 608C and D. MS(APCI(+)) 509 $(M+H)^+$. MS(APCI(-)) 543 $(M+Cl)^-$.



Example 1056D

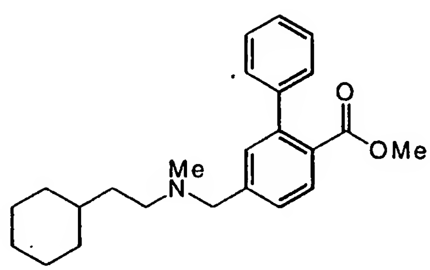
N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine, lithium salt

N-[4-(N-(2-Cyclohexenylethyl)-N-methylaminomethyl)-2-(2-methylphenyl)benzoyl]methionine methyl ester was converted into the title compound by the procedure in example 608E, and was isolated as a white powder.
^{1}H NMR (300 MHz, DMSO) δ 1.38-1.75 (m, 4H), 1.80-2.13 (m, 13H), 1.91 (s, 3H), 2.14 (s, 3H), 2.36-2.45 (m, 2H), 3.50 (s, 2H), 3.56-3.67 (brs, 1H), 5.32-5.36 (m, 1H), 6.88-6.92 (m, 1H), 7.05-7.23 (m, 5H), 7.32 (d, J=8.1 Hz, 1H), 7.48 (d, J=8.1 Hz, 1H).
MS (APCI(-)) m/e 493 (M-H); Analysis calc'd for $C_{29}H_{37}LiN_2O_3S \cdot 1.15H_2O$: C, 66.81; H, 7.60; N, 5.37; found: C, 66.86; H, 7.34; N, 5.19.



Example 1057

N-[4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoyl]methionine, lithium salt



Example 1057A

4-(N-(2-Cyclohexylethyl)-N-methylaminomethyl)-2-phenylbenzoic acid, Methyl Ester

The title compound was prepared according to the procedure in example 608B, replacing 4-bromomethyl-2-(2-methylphenyl)benzoic acid methyl ester with 4-bromomethyl-2-phenylbenzoic acid methyl ester (example 228B).
MS (DCI/NH_3) 366 $(M+H)^+$.